```
=> d his

     (FILE 'HOME' ENTERED AT 13:36:08 ON 05 AUG 2004)

     FILE 'REGISTRY' ENTERED AT 13:36:26 ON 05 AUG 2004
L1           985 S PS/FS AND C2H4O
L2             5 S L1 AND SQL=51
L3            17 S L1 AND SQL=30
L4            15 S L1 AND SQL=21
L5             5 S L1 AND L3 AND L4
                 SAVE L11 TEMP KOSAR/A
                 ACT KOSAR/A
               ---------
L6               STR
L7            26 SEA FILE=REGISTRY SSS FUL L6
                 ---------

     FILE 'CAPLUS' ENTERED AT 13:46:27 ON 05 AUG 2004

     FILE 'REGISTRY' ENTERED AT 13:47:19 ON 05 AUG 2004
                 E INSULIN
                 E INSULIN/CN
L8             1 S E3

     FILE 'CAPLUS' ENTERED AT 13:47:41 ON 05 AUG 2004
L9             3 S L5
L10           12 S L7
L11       135154 S INSULIN OR L8
L12            0 S L10 AND L11
L13            0 S L10 AND INSULIN?/AB

     FILE 'REGISTRY' ENTERED AT 13:48:44 ON 05 AUG 2004

     FILE 'CAPLUS' ENTERED AT 13:49:56 ON 05 AUG 2004
L14           46 S INSULIN (L) OLIGOMER#
L15           12 S L14 AND ORAL?
L16           19 S L14 (L) CONJUG?
L17      1268292 S PEG OR POLYETHYLENE GLYCOL OR POLYMER## OR POLYOXYALKYLENE?
L18           13 S L14 AND L17
L19          483 S L8 (L) L17
L20            6 S L19 (L) OLIGOMER?
L21           42 S L19 (L) CONJUG?
L22            4 S L21 AND OLIGOMER?
L23           13 S L20 OR L22 OR L18
L24           23 S L16 OR L23
```

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 13:57:56 ON 05 AUG 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    3 AUG 2004  HIGHEST RN 721883-12-1
DICTIONARY FILE UPDATES:   3 AUG 2004  HIGHEST RN 721883-12-1

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que stat l5
L1           985 SEA FILE=REGISTRY ABB=ON  PLU=ON  PS/FS AND C2H4O
L3            17 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL=30
L4            15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL=21
L5             5 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND L3 AND L4


=> d que stat l7
L6                STR

    10
    O
    ||
NH--C-- CH2- CH2- CH2-- CH2- CH2- O-- CH2~ CH2
1   2   3   4   5      6   7   8   9     11

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  11

STEREO ATTRIBUTES: NONE
L7            26 SEA FILE=REGISTRY SSS FUL L6

100.0% PROCESSED  88466 ITERATIONS                    26 ANSWERS
SEARCH TIME: 00.00.01


=> fil caplus
FILE 'CAPLUS' ENTERED AT 13:58:26 ON 05 AUG 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
```

FILE COVERS 1907 - 5 Aug 2004 VOL 141 ISS 6
FILE LAST UPDATED: 3 Aug 2004 (20040803/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

```
=> d que nos 19
L1           985 SEA FILE=REGISTRY ABB=ON  PLU=ON  PS/FS AND C2H4O
L3            17 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL=30
L4            15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL=21
L5             5 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND L3 AND L4
L9             3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5

=> d que nos l12
L6               STR
L7            26 SEA FILE=REGISTRY SSS FUL L6
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  INSULIN/CN
L10           12 SEA FILE=CAPLUS ABB=ON  PLU=ON  L7
L11       135154 SEA FILE=CAPLUS ABB=ON  PLU=ON  INSULIN/OBI OR L8
L12            0 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10 AND L11

=> d que nos l13
L6               STR
L7            26 SEA FILE=REGISTRY SSS FUL L6
L10           12 SEA FILE=CAPLUS ABB=ON  PLU=ON  L7
L13            0 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10 AND INSULIN?/AB

=> d que nos l24
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  INSULIN/CN
L14           46 SEA FILE=CAPLUS ABB=ON  PLU=ON  INSULIN/OBI (L) OLIGOMER#/OBI
L16           19 SEA FILE=CAPLUS ABB=ON  PLU=ON  L14 (L) CONJUG?/OBI
L17      1268292 SEA FILE=CAPLUS ABB=ON  PLU=ON  PEG/OBI OR POLYETHYLENE
                 GLYCOL/OBI OR POLYMER##/OBI OR POLYOXYALKYLENE?/OBI
L18           13 SEA FILE=CAPLUS ABB=ON  PLU=ON  L14 AND L17
L19          483 SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 (L) L17
L20            6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L19 (L) OLIGOMER?/OBI
L21           42 SEA FILE=CAPLUS ABB=ON  PLU=ON  L19 (L) CONJUG?/OBI
L22            4 SEA FILE=CAPLUS ABB=ON  PLU=ON  L21 AND OLIGOMER?/OBI
L23           13 SEA FILE=CAPLUS ABB=ON  PLU=ON  L20 OR L22 OR L18
L24           23 SEA FILE=CAPLUS ABB=ON  PLU=ON  L16 OR L23
```

=> d .ca hitstr l9 1-3;d .ca hitstr l24 1-23

L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1986:69169 CAPLUS
DOCUMENT NUMBER: 104:69169
TITLE: Insulin derivatives modified in the B30 position for treating diabetes mellitus
INVENTOR(S): Grau, Ulrich; Geiger, Rolf; Obermeier, Rainer
PATENT ASSIGNEE(S): Hoechst A.-G. , Fed. Rep. Ger.
SOURCE: Ger. Offen., 29 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3334407	A1	19850404	DE 1983-3334407	19830923
EP 137361	A2	19850417	EP 1984-111058	19840917
EP 137361	A3	19870506		
EP 137361	B1	19900516		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
HU 36843	A2	19851028	HU 1984-3491	19840917
AT 52791	E	19900615	AT 1984-111058	19840917
FI 8403695	A	19850324	FI 1984-3695	19840920
DK 8404530	A	19850324	DK 1984-4530	19840921
DK 172632	B1	19990322		
NO 8403799	A	19850325	NO 1984-3799	19840921
AU 8433419	A1	19850328	AU 1984-33419	19840921
AU 573624	B2	19880616		
JP 60094999	A2	19850528	JP 1984-196962	19840921
ZA 8407440	A	19850529	ZA 1984-7440	19840921
ES 536115	A1	19850601	ES 1984-536115	19840921
CA 1247545	A1	19881227	CA 1984-463810	19840921
IL 73021	A1	19890910	IL 1984-73021	19840921

PRIORITY APPLN. INFO.: DE 1983-3334407 A 19830923
EP 1984-111058 A 19840917

AB Bovine, swine, or human insulin derivs. esterified or amidated in the B-30 position were prepared either by condensing a protected des-B23-30-octapeptide insulin with protected H-Gly-Phe-Phe-Tyr-Thr-Pro-Lys-R30-R31 (R30 = genetically codable L-amino acid residue, R31 = substituted amino, alkoxy, etc.), or by treating a Des-(B30)-insulin with H-R30-R31. Thus, treating swine insulin with [(tert-butoxycarbonyl)oxy]succinimide in DMF/Me2SO containing N-ethylmorpholine at room temperature for 6 h, incubating the product with trypsin at 36°, dissolving the resulting 3.25 g NαA1,NαB1-bis-BOC-des-(B23-30)-octapeptide insulin (swine) (BOC = Me3CO2C) along with 100 mg 1-hydroxybenzotriazole, 750 mg HCl.gly-Ph-Phe-Tyr(But)-Thr-Pro-Lys(BOC)-Thr(But)-OPr, and 0.5 mL N-ethylmorpholine in DMF, treating the reaction mixture with dicyclohexylcarbodiimide for 24 h, reacting the product (still protected) with 5 mL F3CCO2H and 1 mL anisole at room temperature for 60 min, and purification of the product using 10% HOAc over SephadexR G50 or G75 gave 1.2 g human insulin-(B30)-OPr. Pharmaceuticals containing swine-(B30)-OMe, human insulin ArgB31-OH, etc., were bioassayed.

IC ICM C07C103-52
ICS A61K037-26

CC 34-4 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63
IT 76688-23-8 80449-79-2 81959-12-8 96351-10-9 **100040-03-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(insulin activity of)
IT **100040-03-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(insulin activity of)
RN 100040-03-7 CAPLUS
CN Poly(oxy-1,2-ethanediyl), α-ethyl-ω-hydroxy-, 30B-ester with insulin (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1983:215966 CAPLUS
DOCUMENT NUMBER: 98:215966
TITLE: Synthesis and spectroscopic characterization of insulin derivatives containing one or two poly(ethylene oxide) chains at specific positions
AUTHOR(S): Ehrat, M.; Luisi, P. L.
CORPORATE SOURCE: Tech.-Chem. Lab., ETH-Zent., Zurich, 8092, Switz.
SOURCE: Biopolymers (1983), 22(1), 569-73
CODEN: BIPMAA; ISSN: 0006-3525
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Poly(ethylene oxide) (PEO) Me ether was converted to MeO(CH2CH2O)nCH2CO2H, which was condensed with NA1, NB29-Msc2-insulin (Msc = MeSO2CH2CH2O2C) and NA1-Msc-insulin and the resulting protected products were Msc-deblocked to give the corresponding NB1-PEO- and NB1,NB29-PEO2-modified insulins. The CD spectra of the latter PEO-modified insulins were altered from that of insulin.
CC 34-3 (Amino Acids, Peptides, and Proteins)
IT 9004-10-8DP, poly(ethylene glycol)-modified derivs. 25322-68-3DP, insulin derivs. **85875-22-5P 85875-23-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and CD of)
IT **85875-22-5P 85875-23-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and CD of)
RN 85875-22-5 CAPLUS
CN Insulin (swine), NB-(hydroxyacetyl)-29B-[N6-(hydroxyacetyl)-L-lysine]-, NB,29B-diether with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 85875-23-6 CAPLUS
CN Insulin (swine), NB-(hydroxyacetyl)-, NB-ether with α-hydro-ω-methoxypoly(oxy-1,2-ethanediyl) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1981:443673 CAPLUS
DOCUMENT NUMBER: 95:43673
TITLE: Insulin derivatives
INVENTOR(S): Obermeier, Rainer; Uhmann, Rainer; Summ, Hans Dieter; Regitz, Guenter; Geisen, Karl
PATENT ASSIGNEE(S): Hoechst A.-G., Fed. Rep. Ger.
SOURCE: Ger. Offen., 13 pp.

CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2930542	A1	19810212	DE 1979-2930542	19790727
EP 27161	A1	19810422	EP 1980-104267	19800719
EP 27161	B1	19830427		
R: AT, BE, CH, DE, FR, GB, IT, NL, SE				
AT 3145	E	19830515	AT 1980-104267	19800719
ES 493550	A1	19810416	ES 1980-493550	19800721
DK 8003243	A	19810128	DK 1980-3243	19800725
JP 56022326	A2	19810302	JP 1980-101370	19800725
CA 1156217	A1	19831101	CA 1980-357096	19800725
PRIORITY APPLN. INFO.:			DE 1979-2930542	19790727
			EP 1980-104267	19800719

AB Insulin was bound to polyethylene glycol monoalkyl ethers via the α-NH2 group of B-chain to give a product that formed aqueous dispersions for parenteral administration and gave >100% effect on blood glucose level with only 65% effect in the fat cell test. Thus, poly(ethylene glycol) monomethyl ether of mol. weight 1500 was treated with OCN(CH2)6NCO and bovine NαA1,NεB29-bis(tert-butoxycarbonyl)insulin and the deblocked to give insulin bound to the poly(ethylene glycol) monomethyl ether via a carbonylaminohexamethyleneaminocarbonyl group.

IC C07C103-52; C07C102-00; A61K037-26

CC 34-3 (Synthesis of Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 63

IT **78337-40-3P 78337-41-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT **78337-40-3P 78337-41-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 78337-40-3 CAPLUS

CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, NB-ester with NB-[[[6-(carboxyamino)hexyl]amino]carbonyl]insulin (cattle) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 78337-41-4 CAPLUS

CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-, NB-ester with NB-[[(6-carboxyhexyl)amino]carbonyl]insulin (swine) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L24 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:392077 CAPLUS
DOCUMENT NUMBER: 140:412315
TITLE: Oral compositions containing active ingredient coated on particles of cellulose or calcium phosphate
INVENTOR(S): Ruff, Michael D.; Cobb, Joseph E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 38 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004091544	A1	20040513	US 2003-643319	20030819
WO 2004043356	A2	20040527	WO 2003-US35075	20031104

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-425024P P 20021108
US 2003-643319 A 20030819

AB Disclosure is an oral formulation containing an active pharmaceutical ingredient, for instance a peptide pharmaceutical, such as insulin, coated onto a suitable particulate substrate, which is not a polysaccharide, such as a cellulose or a calcium phosphate. The oral formulation may be a modified release formulation, for instance a controlled release formulation or a sustained release formulation, or may be an immediate release formulation. Also, the formulation may be encapsulated in gelatin capsules or may be compressed into tablets. The thus obtained dosage forms are especially suitable for delivery of drugs that are incompatible with sugars, such as insulin, due to their polysaccharide-free nature. For example, sustained release gelatin capsules containing polydispersed hexyl insulin monoconjugate 5.8, Emcompress (dicalcium phosphate dihydrate) 209.0, capric acid 22.9, citric acid 46.6, lauric acid 46.6, Opadry YS-1-7006 18.3, sodium cholate 138.4, sodium hydroxide 54.2, sodium phosphate heptahydrate 46.4 and Surelease (Et cellulose) 210.7g was found to have a satisfied performance of insulin delivery as shown by the controlled blood glucose level.

IC ICM A61K009-16
ICS A61K038-00; B01J013-00; A61K009-50
NCL 424490000; 514002000; 427002140
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT **Polyoxyalkylenes**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated oral compns. containing active ingredient coated on particles of calcium phosphate and cellulose)
IT 77-90-7, Acetyl tributyl citrate 77-93-0, Triethyl citrate 471-34-1, Calcium carbonate, biological studies 557-04-0, Magnesium stearate 1592-23-0, Calcium stearate 7693-13-2, Calcium citrate 7757-93-9, Dibasic calcium phosphate 7758-23-8, Monobasic calcium phosphate 7758-87-4, Tribasic calcium phosphate 7778-18-9, Calcium sulfate 7789-77-7, EMCOMPRESS 9004-34-6, Cellets, biological studies 9004-57-3, Surelease 25212-88-8, Eudragit L30D55 25322-68-3, **PEG** 33434-24-1, Eudragit RS30D 117698-04-1, OPADRY YS-1-7006
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coated oral compns. containing active ingredient coated on particles of calcium phosphate and cellulose)
IT 9004-10-8D, **Insulin, oligomer conjugate**

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polydisperse; coated oral compns. containing active ingredient coated on particles of calcium phosphate and cellulose)

L24 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:162445 CAPLUS
DOCUMENT NUMBER: 140:193075
TITLE: Pharmaceutical compositions of **insulin** drug-**oligomer conjugates** and methods of treating diseases therewith
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingam; Ekwuribe, Nnochiri N.; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 235,284.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004038866	A1	20040226	US 2003-382155		20030305
US 2003069170	A1	20030410	US 2002-235284		20020905
US 6770625	B2	20040803			
PRIORITY APPLN. INFO.:			US 2001-318193P	P	20010907
			US 2002-377865P	P	20020503
			US 2002-235281	A2	20020905
			US 2002-235284	A2	20020905

OTHER SOURCE(S): MARPAT 140:193075
AB Pharmaceutical compns. that include insulin, an insulin drug-oligomer conjugate, a fatty acid component, and a bile salt component or a bile salt component without a fatty acid component are described. The insulin drug is covalently coupled to an oligomeric moiety. The fatty acid component and the bile salt component, when together, can be present in a weight-to-weight ratio of between 1:15 and 15:1. Methods of treating an insulin deficiency in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. Substantial redns. in blood glucose were observed as the result of coadministration of hexyl-insulin monoconjugate 2 (HIM2) and bile salts to mice and dogs. All of the bile salts were effective at a level of 1.5 %.
IC ICM A61K038-28
ICS A61K031-57
NCL 514003000; 514171000
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
ST pharmaceutical **insulin** drug **oligomer conjugate** antidiabetic; blood glucose redn **insulin conjugate** bile salt
IT Fatty acids, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C4-20; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)
IT Drug delivery systems

(buccal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Alkanes, biological studies
Oligomers
Polyoxyalkylenes, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**conjugates** with **insulin**; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Digestive tract
(**insulin oligomer conjugate** delivery across wall of; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(liqs., oral; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(liqs.; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(nasal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Antidiabetic agents
Drug delivery systems
(oral; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(parenterals; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Antidiabetic agents
Buffers
Drug delivery systems
Human
Hydrophilicity
Lipophilicity
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Bile salts
Fatty acids, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT **Polyoxyalkylenes**, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(solids; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Flavoring materials
(strawberry; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(tablets; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT Drug delivery systems
(transdermal; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT 9004-10-8, **Insulin**, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(deficiency or disorder, treatment of; pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT 81-24-3 81-25-4 83-44-3 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 145-42-6, Sodium taurocholate 334-48-5, Capric acid 360-65-6 361-09-1, Sodium Cholate 516-50-7 863-57-0 1180-95-6, Sodium taurodeoxycholate 2898-95-5, Sodium ursodeoxycholate 9004-10-8D, **Insulin**, **conjugates** with **oligomers** 11061-68-0D, **Insulin** (human), **conjugates** with methoxy(**polyethylene glycol**) hexanoic acid 11061-68-0D, **Insulin** (human), **conjugates** with polypropylenglycols 25322-68-3D, **Polyethylene glycol**, **conjugates** with **insulin** 116094-23-6D, AspB28insulin, human, **conjugates** with **oligomers** 133107-64-9D, **conjugates** with **oligomers** 326892-09-5D, **conjugates** with human **insulin** 452310-88-2D, **conjugates** with **oligomers** 452310-92-8D, **conjugates** with **oligomers** 452311-02-3D, **conjugates** with **oligomers** 452311-09-0D, **conjugates** with **oligomers** 452311-17-0D, **conjugates** with **oligomers** 452311-24-9D, **conjugates** with **oligomers** 452311-26-1D, **conjugates** with **oligomers** 452311-27-2D, **conjugates** with **oligomers** 452311-29-4D, **conjugates** with **oligomers** 452311-30-7D, **conjugates** with **oligomers** 452311-31-8D, **conjugates** with **oligomers** 452311-32-9D, **conjugates** with **oligomers** 452311-33-0D, **conjugates** with **oligomers** 452311-35-2D, **conjugates** with **oligomers** 452311-36-3D, **conjugates** with **oligomers** 452311-37-4D, **conjugates** with **oligomers** 502487-21-0D, **conjugates** with human **insulin** 502495-36-5D, **conjugates** with **oligomers** 663602-55-9D, **conjugates** with human **insulin** 663602-56-0D, **conjugates** with human **insulin**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates** for treating diseases)

IT 100-44-7, Benzyl chloride, reactions 111-77-3, Diethylene glycol monomethyl ether 112-27-6, Triethylene glycol 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 112-76-5, Stearoyl chloride 124-63-0, Methanesulfonyl chloride 141-78-6, EtOAc, reactions 623-65-4, Palmitic anhydride 865-47-4 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8, Hexaethylene glycol 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6, 8-Bromooctanoic acid 25322-68-3, PEG6 25952-53-8, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer**

conjugates for treating diseases)
IT 3639-35-8P 4437-01-8P, Heptaethylene glycol monomethyl ether
10108-28-8P 24342-68-5P, Hexaethylene glycol monobenzyl ether
29823-21-0P 70802-40-3P 74654-05-0P 86259-87-2P, Tetraethylene
glycol monobenzyl ether 105292-71-5P 124668-93-5P 142556-85-2P
477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P
477775-67-0P 477775-68-1P 477775-69-2P 477775-73-8P 477775-74-9P
477781-68-3P 477781-69-4P 502487-20-9P 502487-21-0P 502487-23-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer**
conjugates for treating diseases)
IT 27425-92-9P, Decaethylene glycol monomethyl ether 62304-85-2P
477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477788-13-9P
502487-22-1P 502487-24-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(pharmaceutical compns. of **insulin** drug-**oligomer**
conjugates for treating diseases)
IT 69-65-8, Mannitol 77-86-1, Tromethamine 77-92-9, Citric Acid,
biological studies 102-71-6, Trolamine, biological studies 557-04-0,
Magnesium Stearate 994-36-5, Sodium Citrate 1310-73-2, Sodium
Hydroxide, biological studies 7558-79-4, Dibasic Sodium Phosphate
7558-80-7, Sodium Phosphate Monobasic 7647-01-0, Hydrochloric Acid,
biological studies 7732-18-5, Water, biological studies 9004-34-6,
Cellulose, biological studies 9063-38-1, Explotab 56038-13-2,
Sucralose 74811-65-7, Croscarmellose Sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer**
conjugates for treating diseases)

L24 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:142842 CAPLUS
DOCUMENT NUMBER: 140:193028
TITLE: Peptide-conjugated oligomeric compounds for enhanced cellular uptake of the oligomers
INVENTOR(S): Manoharan, Muthiah; Maier, Martin
PATENT ASSIGNEE(S): ISIS Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 41 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004034191	A1	20040219	US 2002-222595	20020816
WO 2004016274	A2	20040226	WO 2003-US25567	20030815
WO 2004016274	A3	20040325		
WO 2004016274	B1	20040527		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,

GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2002-222595 A2 20020816
OTHER SOURCE(S): MARPAT 140:193028
AB The invention discloses amphipathic peptide-conjugated oligomeric compds. (e.g. peptide conjugates with oligonucleotides or with peptide nucleic acids), as well as methods of making and using such compds. The invention further discloses methods for enhancing the cellular uptake of oligomeric compds. comprising conjugating the compds. to amphipathic moieties, e.g. amphipathic peptides. Methods for synthesizing the conjugates are included.
IC ICM A61K048-00
ICS C07K009-00; A61K038-14
NCL 530322000; 514008000
CC 1-2 (Pharmacology)
Section cross-reference(s): 33, 34
IT 57-88-5, Cholesterol, biological studies 59-23-4, Galactose, biological studies 59-30-3, biological studies 63-42-3, Lactose 68-19-9, Vitamin B12 3458-28-4, Mannose 7535-00-4, Galactosamine 9004-10-8, **Insulin**, biological studies 9061-61-4, Nerve growth factor 15687-27-1, Ibuprofen 62229-50-9, Epidermal growth factor 99896-85-2, Arginylglycylaspartic acid
RL: BSU (Biological study, unclassified); BIOL (Biological study) (targeting moiety; peptide-**conjugated** oligomeric compds. for enhanced cellular uptake of **oligomers**)

L24 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:1006707 CAPLUS
DOCUMENT NUMBER: 140:35957
TITLE: Methods of reducing hypoglycemic episodes in the treatment of diabetes mellitus by orally administering an **insulin-oligomer conjugate**
INVENTOR(S): Still, James Gordon; Kosutic, Gordana
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003105768	A2	20031224	WO 2003-US18763	20030613
WO 2003105768	A3	20040311		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004038867	A1	20040226	US 2003-461199	20030613

PRIORITY APPLN. INFO.: US 2002-388988P P 20020613
OTHER SOURCE(S): MARPAT 140:35957
AB The present invention provides compns. and methods for reducing

hypoglycemic episodes experienced by a subject in need of treatment for diabetes mellitus, said method comprising orally administering an amount of an insulin polypeptide-oligomer conjugate to the subject, wherein: (i) the amount of the insulin polypeptide-oligomer conjugate reduces the number and/or severity of hypoglycemic episodes experienced by the subject during a given time period when compared with the number and/or severity of hypoglycemic episodes that would have been experienced during a similar time period by the subject or by subjects in a control group parenterally administered insulin, or an insulin analog in an amount that provides a substantially equivalent level of glycemic control; and (ii) the oligomer of the insulin polypeptide-oligomer conjugate comprises a hydrophilic moiety and a lipophilic moiety. Patients with type 1 diabetes were treated p.o. with HIM2 (human insulin with -C(O)(CH2)5(OC2H4)7OCH3 conjugated to the B29 lysine) in comparison with treatment with insulin lispro, s.c. Hypoglycemic events that required rescue intervention were significantly lower in the HIM2 treatment group as compared to the insulin lispro treatment group.

IC ICM A61K

CC 1-10 (Pharmacology)
Section cross-reference(s): 63

ST **insulin conjugate** reducing hypoglycemic episode
diabetes mellitus; oral **insulin oligomer conjugate** hypoglycemia redn antidiabetic; HIM2 oral antidiabetic redn hypoglycemic episode

IT Drug delivery systems
(capsules; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT **Oligomers**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic-lipophilic, **conjugates** with **insulin**; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Diabetes mellitus
(**insulin**-dependent; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Drug delivery systems
(liqs., oral; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Hydrophilicity
Lipophilicity
(of **oligomer**; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Diabetes mellitus
Human
Hypoglycemia
Postprandial period
(oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Antidiabetic agents
(oral; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT Flavoring materials
(strawberry; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 50-99-7, D-Glucose, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HIM2 **conjugate** maintenance of two-hour postprandial blood levels of; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 9035-68-1, Proinsulin
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation **conjugation** of; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 9002-07-7, Trypsin 9025-24-5, Carboxypeptidase B
RL: CAT (Catalyst use); USES (Uses)
(in HIM2 **conjugate** preparation from proinsulin; oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 223714-27-0P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 9004-10-8D, **Insulin**, **conjugates** with hydrophilic-lipophilic **oligomer** 502487-21-0D, **conjugates** with **insulin**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

IT 57-55-6, Propylene glycol, biological studies 77-86-1, Tris(hydroxymethyl)aminomethane 77-92-9, Citric acid, biological studies 102-71-6, Triethanolamine, biological studies 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 334-48-5, Capric acid 361-09-1, Sodium cholate 1310-73-2, Sodium hydroxide, biological studies 7632-05-5, Sodium phosphate 7732-18-5, Water, biological studies 56038-13-2, Sucralose
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral **insulin-oligomer conjugate** for reducing hypoglycemic episodes in treatment of diabetes mellitus)

L24 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:971710 CAPLUS
DOCUMENT NUMBER: 140:16981
TITLE: Methods of synthesizing **insulin** polypeptide-**oligomer conjugates** and proinsulin polypeptide-**oligomer conjugates**
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingam; Ekwuribe, Nnochiri N.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 101 pp., Cont.-in-part of U.S. Pat. Appl. 2003 87,808.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003229009	A1	20031211	US 2003-382022	20030305
US 2003087808	A1	20030508	US 2001-36744	20011221
US 2003228652	A1	20031211	US 2003-389499	20030317

PRIORITY APPLN. INFO.: US 2001-318197P P 20010907
US 2001-36744 A2 20011221
US 2003-382022 A2 20030305

OTHER SOURCE(S): MARPAT 140:16981

AB The invention provides a method for synthesizing an insulin polypeptide-oligomer conjugate that includes contacting a proinsulin polypeptide, comprising an insulin polypeptide coupled to one or more peptides by peptide bond(s) capable of being cleaved to yield the insulin polypeptide, with an oligomer under conditions sufficient to couple the oligomer to the insulin polypeptide portion of the proinsulin polypeptide and provide a proinsulin polypeptide-oligomer conjugate, and cleaving the one or more peptides from the proinsulin polypeptide-oligomer conjugate to provide the insulin polypeptide-oligomer conjugate.

IC ICM A61K038-28
ICS C07K014-62

NCL 514003000; 530303000

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 2

IT Antidiabetic agents
Drug delivery systems
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 9004-10-8DP, **Insulin**, **conjugates** 9035-68-1DP, Proinsulin, **conjugates**
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 56-87-1, Lysine, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 9002-07-7, Trypsin 9025-24-5, Carboxy peptidase b
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 623-65-4, Palmitic anhydride 865-47-4 5299-60-5, Ethyl 6-hydroxyhexanoate 17696-11-6, 8-Bromooctanoic acid 24342-68-5, Hexaethylene glycol monobenzyl ether 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 4437-01-8P, Heptaethylene glycol monomethyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 74654-05-0P 124668-93-5P 130955-39-4P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477781-68-3P 502487-20-9P 502487-21-0P 502487-22-1P 502487-24-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of **insulin** polypeptide-**oligomer**

conjugates and proinsulin polypeptide-**oligomer** **conjugates**)

IT 59112-80-0D, c Peptide, **conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

L24 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:971618 CAPLUS
DOCUMENT NUMBER: 140:16980
TITLE: Methods of synthesizing **insulin** polypeptide-**oligomer conjugates** and proinsulin polypeptide-**oligomer conjugates**
INVENTOR(S): Radhakrishnan, Balasingam; Soltero, Richard; Ekwuribe, Nnochiri N.; Puskas, Monica; Sangal, Diti
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 102 pp., Cont.-in-part of U.S. Ser. No. 382,022.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003228652	A1	20031211	US 2003-389499		20030317
US 2003087808	A1	20030508	US 2001-36744		20011221
US 2003229009	A1	20031211	US 2003-382022		20030305
PRIORITY APPLN. INFO.:			US 2001-318197P	P	20010907
			US 2001-36744	A2	20011221
			US 2003-382022	A2	20030305

OTHER SOURCE(S): MARPAT 140:16980
AB The invention provides a method for synthesizing an insulin polypeptide-oligomer conjugate that includes contacting a proinsulin polypeptide, comprising an insulin polypeptide coupled to one or more peptides by peptide bond(s) capable of being cleaved to yield the insulin polypeptide, with an oligomer under conditions sufficient to couple the oligomer to the insulin polypeptide portion of the proinsulin polypeptide and provide a proinsulin polypeptide-oligomer conjugate, and cleaving the one or more peptides from the proinsulin polypeptide-oligomer conjugate to provide the insulin polypeptide-oligomer conjugate.
IC ICM C12P021-06
ICS A61K038-28
NCL 435068100; 530303000
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 2
IT Antidiabetic agents
Drug delivery systems
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)
IT 9004-10-8DP, **Insulin**, **conjugates** 9035-68-1DP, Proinsulin, **conjugates**
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer**

conjugates)
IT 56-87-1, Lysine, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)
IT 9002-07-7, Trypsin 9025-24-5, Carboxy peptidase b
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)
IT 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 623-65-4, Palmitic anhydride 865-47-4 5299-60-5, Ethyl 6-hydroxyhexanoate 17696-11-6, 8-Bromooctanoic acid 24342-68-5, Hexaethylene glycol monobenzyl ether 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)
IT 4437-01-8P, Heptaethylene glycol monomethyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 74654-05-0P 124668-93-5P 130955-39-4P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477781-68-3P 502487-20-9P 502487-21-0P 502487-22-1P 502487-24-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)
IT 59112-80-0D, c Peptide, **conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

L24 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:634930 CAPLUS
TITLE: Evaluation of molecular weight distribution of poly-dispersed **insulin oligomer** **conjugate** (HIM2 poly-dispersed)
AUTHOR(S): Sangal, Diti; Puskas, Monica; Krishnan, B. Radha
CORPORATE SOURCE: Chemistry Development and Manufacturing, Nobex, Durham, NC, 27713, USA
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-322. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The purpose of this study was to isolate and identify polyethylene glycol (PEG) mol. weight distribution pattern in the poly-dispersed amphiphilic oligomer conjugated at B29-Lys of insulin, HIM2 (poly-dispersed). The conjugate was analyzed by reverse phase HPLC for evaluation of PEG distribution pattern. A semi-preparative reverse phase HPLC method provided separation of individual mol. weight forms from the polymeric HIM2 (poly-dispersed). These discreet mol. wts. were characterized by MALDI

(TOF) and will be studied by s.c. mouse glucose assay. The PEG distribution of HIM2 (poly-dispersed) ranged from PEG4 to PEG12 with PEG7, PEG8 and PEG9 accounting for approx. 70% of HIM2 (poly-dispersed) composition Reverse phase HPLC (poly-dispersed) method using high concentration of TFA allowed separation of discreet PEG mol. wts. of HIM2 (poly-dispersed). As previously mentioned, the biol. potency of these discreet separated PEG mol. wts. of HIM2 (poly-dispersed) will be studied using a s.c. mouse glucose assay.

L24 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:570791 CAPLUS
DOCUMENT NUMBER: 139:122771
TITLE: Use of oligomers and **polymers** for drug solubilization, stabilization, and delivery
INVENTOR(S): Soane, David S.; Suich, Daniel J.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003059321	A1	20030724	WO 2002-US41416	20021223
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003180244	A1	20030925	US 2002-328898	20021223
PRIORITY APPLN. INFO.:			US 2001-343483P P	20011221

AB The use of oligomers and polymers capable of rendering insol. drugs soluble, protecting unstable drugs, and facilitating the delivery of drugs to their site of action is described. A "smart" surfactant is provided comprising a hydrophobic element, e.g., a small mol. or an oligomer or polymer, covalently attached to a hydrophilic element, capable of forming a micelle that encapsulates a hydrophobic drug. This invention further relates to processes for the preparation of such oligomers and polymers, and to compns. containing them. For example, oral delivery of insulin by transcytosis was presented. Insulin is conjugated to a polar loading element of a smart surfactant for the formation of polar-core micelles with the insulin contained in the core. The hydrophobic element of the smart surfactant is comprised of a hydrophobic peptoid oligomer, and the hydrophilic element contains an ester linkage which is a substrate for intestinal lipase. The micelles protect the insulin from the degradative enzymes and gastric pH. The micelles travel to the small intestine, where lipases cleave the ester linkage in the hydrophilic element. The cleavage of this linker unmasks the monosaccharide ligand, which then binds to lectins present on the apical membrane surface of mucosal enterocyte, localizing the micelles to the cells. The micelles then cross the mucosal enterocytes by receptor-mediated transcytosis induced by the binding of the ligand to the lectin, which transports the micelles to the bloodstream. Gradual

decomposition of the micelles, initiated by cleavage of the hydrophilic element, results in the release of insulin into the bloodstream.

IC ICM A61K009-127
ICS A61K009-14; A61K009-50; A61K009-20; A61F013-00

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2, 33, 34

ST **polymer** surfactant drug solubilization stabilization delivery; oligomer surfactant drug solubilization stabilization delivery; protein drug encapsulation surfactant micelle

IT Hepatitis
(C, oral delivery of antiviral ribozyme for treatment of; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Hepatitis C virus
(E2 protein, oral delivery; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(E2, hepatitis C, oral delivery; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Ribozymes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiviral, oral delivery to hepatitis C-infected liver cells; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Amino acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aromatic; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Stem cell
(bone marrow, artificial chromosomes i.v. delivery to; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Nervous system
(central, hydrophobic drug i.v. delivery to; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Neoplasm
(cholera toxin A subunit i.v. delivery to; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cholera, A subunit, i.v. delivery to tumor; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Peptides, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates, with oligosaccharides; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Oligosaccharides, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates, with peptides; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dihydropyridine, of blood-brain barrier, micelles binding to; oligomers and **polymers** for drug solubilization,

stabilization, and delivery by micellization)
IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drugs; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Intestine
(enterocyte, protein drug oral delivery by; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Blood-brain barrier
(hydrophobic drug crossing of; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Artificial chromosome
(i.v. delivery to bone marrow stem cells; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Enzymes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Drug delivery systems
(injections, i.v.; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Agglutinins and Lectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ligands for; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Brain, neoplasm
(methotrexate i.v. delivery to; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Self-assembly
(micelles formation by; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Regeneration, animal
(neuron, hydrophobic drug i.v. delivery for; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Nerve
(neuron, regeneration, hydrophobic drug i.v. delivery for; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Encapsulation
(oligomers and **polymers** for drug solubilization, stabilization, and delivery by micelle encapsulation)
IT Micelles
Permeation enhancers
Solubilizers
Stabilizing agents
Surfactants
(oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Bile acids
Oligomers
Oligosaccharides, biological studies
Peptides, biological studies
Polymers, biological studies
Polysaccharides, biological studies
Steroids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligomers and **polymers** for drug solubilization,

stabilization, and delivery by micellization)
IT Drug delivery systems
(oral; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Drug delivery systems
(prodrugs; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Peptides, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pseudopeptides, peptoids; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Transcytosis
(receptor-mediated, **insulin** oral delivery by; **oligomers** and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Macrophage
(repressor protein i.v. delivery to cytoplasm of; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Steroids, biological studies
Triterpenes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sapogenins; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Stomach
(small mol. drugs oral delivery by; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Intestine
(small, protein drugs oral delivery by; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Bone marrow
(stem cells, artificial chromosomes i.v. delivery to; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Sapogenins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(steroidal; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT Sapogenins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(triterpenoid; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT 59-05-2, Methotrexate 59865-13-3, Cyclosporin A
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. delivery to CNS; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT 9001-92-7, Protease
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT 2667-02-9DP, conjugates with oligosaccharides 564474-54-0DP, conjugates with oligosaccharides
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT 50-99-7, D-Glucose, biological studies 57-88-5, Cholesterol, biological studies 9004-53-9, Dextrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(oligomers and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT **9004-10-8**, **Insulin**, biological studies 11096-26-7, Erythropoietin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral delivery; **oligomers** and **polymers** for drug solubilization, stabilization, and delivery by micellization)
IT **9004-10-8**, **Insulin**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral delivery; **oligomers** and **polymers** for drug solubilization, stabilization, and delivery by micellization)
RN 9004-10-8 CAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:221806 CAPLUS
DOCUMENT NUMBER: 138:260413
TITLE: Methods of synthesizing **insulin** polypeptide-**oligomer conjugates**, and proinsulin polypeptide-**oligomer conjugates** and methods of synthesizing same
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingham; Ekwuribe, Nnochiri N.
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022996	A2	20030320	WO 2002-US28428	20020906
WO 2003022996	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003087808	A1	20030508	US 2001-36744	20011221
EP 1430082	A2	20040623	EP 2002-766246	20020906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:

US 2001-318197P	P	20010907
US 2001-36744	A	20011221
US 2002-349462P	P	20020118
WO 2002-US28428	W	20020906

OTHER SOURCE(S): MARPAT 138:260413
AB Methods for synthesizing proinsulin polypeptides are described that

include a contacting a proinsulin polypeptide including an insulin polypeptide coupled to one or more peptides by peptide bond(s) capable of being cleaved to yield the insulin polypeptide with an oligomer under conditions sufficient to couple the oligomer to the insulin polypeptide portion of the proinsulin polypeptide and provide a proinsulin polypeptide-oligomer conjugate, and cleaving the one or more peptides from the proinsulin polypeptide-oligomer conjugate to provide the insulin polypeptide-oligomer conjugate. Methods of synthesizing proinsulin polypeptide-oligomer conjugates are also described as are proinsulin polypeptide-oligomer conjugates. Methods of synthesizing C-peptide polypeptide-oligomer conjugates are also described.

IC ICM C12N

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 2

IT Antidiabetic agents
Drug delivery systems
(synthesizing **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 9004-10-8DP, **Insulin**, **conjugates** 9035-68-1DP, Proinsulin, **conjugates**
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesizing **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 56-87-1, Lysine, biological studies
RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)
(synthesizing **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 9002-07-7, Trypsin 9025-24-5, Carboxy peptidase b
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(synthesizing **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 111-77-3, Diethylene glycol monomethyl ether 112-35-6, Triethylene glycol monomethyl ether 112-60-7, Tetraethylene glycol 623-65-4, Palmitic anhydride 865-47-4 5299-60-5, Ethyl 6-hydroxyhexanoate 17696-11-6, 8-Bromooctanoic acid 24342-68-5, Hexaethylene glycol monobenzyl ether 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesizing **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 4437-01-8P, Heptaethylene glycol monomethyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 74654-05-0P 124668-93-5P 130955-39-4P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-70-5P 477775-76-1P 477775-77-2P 477781-68-3P 502487-20-9P 502487-21-0P 502487-22-1P 502487-24-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesizing **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

IT 59112-80-0D, c Peptide, **conjugates**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(synthesizing **insulin** polypeptide-**oligomer** **conjugates** and proinsulin polypeptide-**oligomer** **conjugates**)

L24 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:221462 CAPLUS
DOCUMENT NUMBER: 138:260437
TITLE: Pharmaceutical compositions of drug-oligomer conjugates for oral administration
INVENTOR(S): Soltero, Richard; Ekwuribe, Nnochiri N.; Opawale, Foyeke; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022210	A2	20030320	WO 2002-US28536	20020906
WO 2003022210	A3	20031218		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003083232	A1	20030501	US 2002-235381	20020905
PRIORITY APPLN. INFO.:			US 2001-318193P P	20010907
			US 2002-377865P P	20020503

AB An oral pharmaceutical composition comprising a drug-oligomer conjugate, 0.1-15% of a fatty acid component, and 0.1-15% of a bile salt component is described. The drug, e.g., a peptide or protein, is covalently coupled to an oligomeric moiety. The fatty acid component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating diseases in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. For example, tablets containing an insulin conjugate HIM2 were prepared by lyophilization of a mixture containing HIM2 2.5 g, Na cholate 30.0 g, oleic acid 10.0 g, 25% sucralose 8.0 g, flavor 4.0 g, capric acid 5.0 g, lauric acid 5.0 g, citric acid 67.2 g, trolamine 42.4 g, NaOH 18.8 g, pH adjusters (5N NaOH and 5N HCl) as needed, and water resulting in an amorphous powder. The powder (127.6 g) was blended with citric acid 29.7 g, sodium citrate 84.2 g, Tris base 106.7 g, microcryst. cellulose 24.8 g, and Explotab 9.4 g and compressed into tablets.

IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 35
IT 11061-68-0D, Human **insulin**, **conjugates** with methoxy(**polyethylene glycol**) hexanoic acid 326892-09-5D, **conjugates** with human **insulin**

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. of drug-**oligomer conjugates** containing bile salt and fatty acid)

L24 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:221460 CAPLUS
DOCUMENT NUMBER: 138:260435
TITLE: Pharmaceutical compositions of **insulin** drug-**oligomer conjugates**
INVENTOR(S): Soltero, Richard; Radhakrishnan, Balasingham; Ekwuribe, Nnochiri N.; Rehlaender, Bruce; Hickey, Anthony; Bovet, Li Li
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022208	A2	20030320	WO 2002-US28429	20020906
WO 2003022208	A3	20030925		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003083232	A1	20030501	US 2002-235381	20020905
PRIORITY APPLN. INFO.:			US 2001-318193P P	20010907
			US 2002-377865P P	20020503

OTHER SOURCE(S): MARPAT 138:260435
AB Pharmaceutical compns. that include an insulin drug-oligomer conjugate, a fatty acid component, and a bile salt component are described. The insulin drug is covalently coupled to an oligomeric moiety. The fatty acid component and the bile salt component are present in a weight-to-weight ratio of between 1:5 and 5:1. Methods of treating an insulin deficiency in a subject in need of such treatment using such pharmaceutical compns. are also provided, as are methods of providing such pharmaceutical compns. E.g., PEG derivs. of fatty acids such as hexanoic acid were prepared, activated and conjugated to insulin derivs.
IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 34, 35
ST insulin **PEG** fatty acid conjugate pharmaceutical
IT Drug delivery systems
(oral; pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)
IT Drug delivery systems
(solids; pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)
IT 361-09-1, Sodium cholate

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 111-77-3 112-35-6 112-60-7 112-76-5, Stearoyl chloride 623-65-4, Palmitic anhydride 2615-15-8 15848-88-1 23601-40-3, 2,5,8,11,14,17-Hexaoxanonadecan-19-ol 142556-85-2 477788-13-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 3639-35-8P, Decanoic acid, 10-hydroxy-, ethyl ester 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 5299-60-5P, Ethyl 6-hydroxyhexanoate 10108-28-8P 24342-68-5P, Hexaethylene glycol monobenzyl ether 27425-92-9P, Decaethylene glycol monomethyl ether 29823-21-0P, Ethyl 8-bromooctanoate 60037-74-3P 74654-05-0P 86259-87-2P 105292-71-5P 113395-48-5P 124668-93-5P 259228-98-3P 477775-57-8P 477775-58-9P 477775-59-0P 477775-60-3P 477775-65-8P 477775-66-9P 477775-68-1P 477775-69-2P 477775-70-5P 477775-73-8P 477775-74-9P 477775-75-0P 477775-76-1P 477775-77-2P 477781-68-3P 477781-69-4P 502487-20-9P 502487-21-0P 502487-22-1P 502487-23-2P 502487-24-3P 502487-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT **9004-10-8DP**, **Insulin**, **conjugates** with fatty acid-**PEG** derivs.
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT 502495-05-8 502495-19-4 502495-22-9 502495-24-1 502495-25-2 502495-35-4 502495-36-5 502495-38-7 502495-39-8 502495-40-1 502495-41-2 502495-42-3 502495-43-4 502495-44-5 502495-47-8 502495-48-9 502495-51-4 502495-52-5 502495-53-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

IT **9004-10-8DP**, **Insulin**, **conjugates** with fatty acid-**PEG** derivs.
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. of **insulin** drug-**oligomer conjugates**)

RN 9004-10-8 CAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L24 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:184235 CAPLUS
TITLE: Effects of amphiphilic **oligomers** on oral **insulin conjugates.** Part 3: Solubility and protease stability
AUTHOR(S): James, Kenneth D.; Willie, Kirsten; Malkar, Navdeep B.; Severynse-Stevens, Diana; Ekwuribe, Nnochiri N.
CORPORATE SOURCE: Innovation and Drug Discovery, Nobex Corporation, Durham, NC, 27713, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003),

MEDI-269. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The conjugation of polymers (such as polyethylene glycol; PEG) to peptide therapeutics has been known to increase the aqueous solubility and the circulation time of the parent peptide. Although the resultant peptide conjugate may have an improved pharmacodynamic profile, the large oligomers that are commonly used preclude oral delivery of the therapeutic. Nobex Corporation has proprietary amphiphilic oligomers (polyoxyethylene alkyl ethers) that have been applied to several peptide therapeutics to enhance their PK/PD profile and enable oral delivery. We now present a study of the SAR and physicochem. properties of a series of insulin conjugates in which the oligomers vary in size, sterics, and amphiphilic balance. In Part 3 of this study, we assess the effects of various oligomers on solubility at varying pH and salt concns. We also evaluate stability of the resultant conjugates to the digestive enzymes trypsin, chymotrypsin, and pepsin.

L24 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:184234 CAPLUS
TITLE: Effects of amphiphilic **oligomers** on oral **insulin conjugates.** Part 2: Conformational changes of **conjugates**
AUTHOR(S): Malkar, Navdeep; Juska, Darius; Fields, Gregg B.; Ekwuribe, Nnochiri N.; James, Kenneth D.
CORPORATE SOURCE: Nobex Corporation, Research Triangle Park, NC, 27709, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-268. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Amphipathic α-helixes are ubiquitous structural features observed in biol. active peptides. They play important roles in the folding, protein-protein recognition, and protein-membrane interaction of peptides. The conjugation of amphiphilic oligomers (polyoxyethylene alkyl ethers) to peptide therapeutics has been known to alter the biol. activity of the parent peptide. This may be due to alterations in the protein folding or to conformational changes in the peptide. In Part 2 of our study, we report results from CD Spectroscopy (CD) and Differential Scanning Calorimetry (DSC) of different insulin conjugates. We evaluated the effect of our amphiphilic oligomers, which vary in their size, sterics, and amphiphilic balance on the conformational changes of oral insulin conjugates in solution by CD. The deconvolution analyses of the conjugates were also performed. The thermal denaturation (Tm) of these insulin conjugates was determined by CD and DSC.

L24 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:184233 CAPLUS
TITLE: Effects of amphiphilic **oligomers** on oral **insulin conjugates**
AUTHOR(S): Miller, Mark A.; Malkar, Navdeep B.; Odenbaugh, Amy L.; Surguladze, David; Danek Burgess, Krisstina S.; Bednarcik, Mark J.; Dugdell, Robert E.; Yarbrough, Kevin G.; Willie, Kirsten; Ekwuribe, Nnochiri N.;

James, Kenneth D.
CORPORATE SOURCE: Nobex Corporation, Research Triangle Park, NC, 27709, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-267. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB In an effort to understand the effects of conjugating amphiphilic oligomers to insulin, a broad range of oligomers, varying in their amphiphilicity, length, and structure, were synthesized and conjugated to insulin. The physicochem. properties of the insulin conjugates, including in vitro and in vivo activity, were examined Part 1 of our study describes the synthesis of the oligomers and the activity results of the insulin conjugates. The in vitro assays measure agonist activity at the insulin receptor and the in vivo efficacy was assayed by oral dosing in mice. Our goal with this research is to establish a guide to generally predict the effects of amphiphilic oligomers not only on insulin, but on other proteins and peptides, thus facilitating the oral delivery of protein and peptide conjugates.

L24 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:946130 CAPLUS
DOCUMENT NUMBER: 138:29120
TITLE: Preparation of peptide drug-alkylene glycol oligomer conjugates
INVENTOR(S): Ekwuribe, Nnochiri N.; Price, Christopher H.; Ansari, Aslam M.; Odenbaugh, Amy L.
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002098446	A1	20021212	WO 2002-US17567	20020604
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003228275	A1	20031211	US 2001-873797	20010604
BR 2001006401	A	20030211	BR 2001-6401	20011011
JP 2003104913	A2	20030409	JP 2001-317307	20011015
EP 1404355	A1	20040407	EP 2002-737357	20020604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2001-873797 A 20010604
WO 2002-US17567 W 20020604
OTHER SOURCE(S): MARPAT 138:29120

AB A non-polydispersed mixture of conjugates in which each conjugate in the mixture comprises a peptide drug coupled to an oligomer that includes a polyalkylene glycol moiety is disclosed. The mixture may exhibit higher in vivo activity than a polydispersed mixture of similar conjugates. The mixture may be more effective at surviving an in vitro model of intestinal digestion than polydispersed mixts. of similar conjugates. The mixture may result in less inter-subject variability than polydispersed mixts. of similar conjugates. Thus, non-polydispersed hexaethylene glycol was treated with phosgene solution, followed by treatment with N-hydroxysuccinimide (NHS) to give give the NHS ester. Human growth hormone (Saizen) was allowed to react with the NHS ester to give the conjugate.

IC ICM A61K038-02
ICS A61K038-18; A61K038-19; A61K038-22; A61K038-23; A61K038-28; A61K039-385; C07K001-113; C07K002-00; C07K014-475; C07K014-52; C07K014-575; C07K014-585

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 37

IT **Polyoxyalkylenes**, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates, with peptide drugs; preparation of peptide drug-alkylene glycol oligomer conjugates)

IT **Polyoxyalkylenes**, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of peptide drug-alkylene glycol oligomer conjugates)

IT 57-10-3, Palmitic acid, reactions 75-44-5, Phosgene 111-77-3 112-27-6, Triethylene glycol 112-35-6 112-76-5, Octadecanoyl chloride 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 25322-68-3, **Polyethylene glycol** 74124-79-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of peptide drug-alkylene glycol oligomer conjugates)

IT 58-82-2DP, Bradykinin, conjugates with alkylene glycols 1407-47-2DP, Angiotensin, conjugates with alkylene glycols 8049-62-5DP, Zinc **insulin**, **conjugates** with alkylene glycols 9002-60-2DP, ACTH, conjugates with alkylene glycols 9002-76-0DP, Gastrin, conjugates with alkylene glycols 9002-79-3DP, Melanocyte stimulating hormone, conjugates with alkylene glycols 9004-10-8DP, **Insulin**, **conjugates** with alkylene glycols 9007-92-5DP, Glucagon, conjugates with alkylene glycols 9011-97-6DP, Cholecystokinin, conjugates with alkylene glycols 9015-71-8DP, Corticotropin releasing factor, conjugates with alkylene glycols 9015-94-5DP, Renin, conjugates with alkylene glycols 9034-40-6DP, LHRH, conjugates with alkylene glycols 11000-17-2DP, Vasopressin, conjugates with alkylene glycols 11061-68-0DP, Human **insulin**, **conjugates** with alkylene glycols 12629-01-5DP, Human growth hormone, conjugates with alkylene glycols 24305-27-9DP, Thyrotropin-releasing hormone, conjugates with alkylene glycols 31362-50-2DP, Bombesin, conjugates with alkylene glycols 33507-63-0DP, Substance P, conjugates with alkylene glycols 37221-79-7DP, Vasoactiveintestinal peptide, conjugates with alkylene glycols 47931-85-1DP, Salmon calcitonin, conjugates with alkylene glycols 51110-01-1DP, Somatostatin, conjugates with alkylene glycols 52906-92-0DP, Motilin, conjugates with alkylene glycols 57285-09-3DP, Inhibin, conjugates with alkylene glycols 58391-28-9DP, Leucokinin, conjugates with alkylene glycols 59112-80-0DP, C-Peptide, conjugates

with alkylene glycols 60118-07-2DP, Endorphin, conjugates with alkylene glycols 72093-21-1DP, Mastoparan, conjugates with alkylene glycols 74135-04-9DP, Morphiceptin, conjugates with alkylene glycols 74913-18-1DP, Dynorphin, conjugates with alkylene glycols 77614-16-5DP, Dermorphin, conjugates with alkylene glycols 83652-28-2DP, Calcitonin gene related peptide, conjugates with alkylene glycols 83856-13-7DP, Mast cell degranulating peptide, conjugates with alkylene glycols 85568-32-7DP, Casomorphin, conjugates with alkylene glycols 85637-73-6DP, Atrial natriuretic peptide, conjugates with alkylene glycols 106602-62-4DP, Amylin, conjugates with alkylene glycols 107666-54-6DP, GNRH associated peptide, conjugates with alkylene glycols 110119-33-0DP, Allatostatin, conjugates with alkylene glycols 114471-18-0DP, Brain natriuretic peptide, conjugates with alkylene glycols 116243-73-3DP, Endothelin, conjugates with alkylene glycols 119418-04-1DP, Galanin, conjugates with alkylene glycols 127830-04-0DP, C-Type natriuretic peptide, conjugates with alkylene glycols 144940-98-7DP, Guanylin, conjugates with alkylene glycols 154835-90-2DP, Adrenomedullin, conjugates with alkylene glycols 169494-85-3DP, Leptin, conjugates with alkylene glycols 193829-96-8DP, Cortistatin, conjugates with alkylene glycols 259228-98-3DP, peptide drug conjugates 477775-63-6DP, peptide drug conjugates 477775-66-9DP, peptide drug conjugates 477775-70-5DP, peptide drug conjugates 477775-72-7DP, peptide drug conjugates 477775-76-1DP, peptide drug conjugates 477775-77-2DP, peptide drug conjugates 477788-13-9DP, peptide drug conjugates
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide drug-alkylene glycol **oligomer conjugates**)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:946037 CAPLUS
DOCUMENT NUMBER: 138:16621
TITLE: Preparation of **insulin**-alkylene glycol **oligomer conjugates**
INVENTOR(S): Ekwuribe, Nnochiri N.; Price, Christopher H.; Ansari, Aslam M.; Odenbaugh, Amy L.; Radhakrishnan, Balasingam
PATENT ASSIGNEE(S): Nobex Corporation, USA
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002098232	A1	20021212	WO 2002-US17574	20020604
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003027748	A1	20030206	US 2001-873899	20010604

BR 2001006851 A 20030408 BR 2001-6851 20011011
JP 2003113113 A2 20030418 JP 2001-316998 20011015
EP 1404178 A1 20040407 EP 2002-737359 20020604
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2001-873899 A 20010604
WO 2002-US17574 W 20020604

OTHER SOURCE(S): MARPAT 138:16621

AB A mixture of conjugates in which each conjugate in the mixture comprises an insulin drug coupled to an oligomer that includes a polyalkylene glycol moiety is disclosed. The mixture may exhibit higher in vivo activity than a polydispersed mixture of similar conjugates. The mixture may also be more effective at surviving an in vitro model of intestinal digestion than polydispersed mixts. of similar conjugates. The mixture may also result in less inter-subject variability than polydispersed mixts. of similar conjugates. Thus, non-polydispersed hexaethylene glycol was treated with phosgene solution, followed by treatment with N-hydroxysuccinimide (NHS) to give give the NHS ester. Human insulin was dissolved in DMSO and allowed to react with the NHS ester to give the conjugate.

IC ICM A01N061-00
ICS A01N037-18; A61K031-00; A61K038-00; A61K038-28

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 37

ST **insulin** alkylene glycol **oligomer conjugate** prepn

IT **Polyoxyalkylenes**, biological studies
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**conjugates**; preparation of **insulin**-alkylene glycol **oligomer conjugates**)

IT **Polyoxyalkylenes**, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of **insulin** -alkylene glycol **oligomer conjugates**)

IT Drug delivery systems
Human
Molecular weight distribution
(preparation of **insulin**-alkylene glycol **oligomer conjugates**)

IT 57-10-3, Palmitic acid, reactions 75-44-5, Phosgene 111-77-3 112-35-6 112-60-7, Tetraethylene glycol 112-76-5, Octadecanoyl chloride 1679-53-4, 10-Hydroxydecanoic acid 2615-15-8 5299-60-5, Ethyl 6-hydroxyhexanoate 6066-82-6, N-Hydroxysuccinimide 17696-11-6 25322-68-3, **Polyethylene glycol** 74124-79-1 142556-85-2 477775-62-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of **insulin** -alkylene glycol **oligomer conjugates**)

IT 3639-35-8P 4437-01-8P, 2,5,8,11,14,17,20-Heptaoxadocosan-22-ol 9004-74-4P 9004-99-3P 24342-68-5P 29823-21-0P 62304-85-2P 70802-40-3P 74654-05-0P 86259-87-2P 87117-61-1P 105292-71-5P 124668-93-5P 175172-61-9P 477775-58-9P 477775-59-0P 477775-60-3P 477775-61-4P 477775-65-8P 477775-67-0P 477775-68-1P 477775-69-2P 477775-71-6P 477775-73-8P 477775-74-9P 477775-75-0P 477781-68-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in alkylene glycol derivs. preparation; preparation of **insulin** -alkylene glycol **oligomer conjugates**)

IT 8049-62-5DP, Zinc **Insulin**, alkylene glycol **oligomer**

conjugates 9004-10-8DP, **Insulin**, alkylene glycol **oligomer conjugates** 11061-68-0DP, Human **insulin**, alkylene glycol **oligomer conjugates** 259228-98-3DP, **insulin conjugates** 477775-63-6DP, **insulin conjugates** 477775-66-9DP, **insulin conjugates** 477775-70-5DP, **insulin conjugates** 477775-72-7DP, **insulin conjugates** 477775-76-1DP, **insulin conjugates** 477775-77-2DP, **insulin conjugates**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **insulin**-alkylene glycol **oligomer conjugates**)

IT 477775-63-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **insulin**-alkylene glycol **oligomer conjugates**)

IT 259228-98-3P 477775-66-9P 477775-70-5P 477775-72-7P 477775-76-1P 477775-77-2P 477788-13-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **insulin**-alkylene glycol **oligomer conjugates**)

IT 477788-13-9DP, **insulin conjugates**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **insulin**-alkylene glycol **oligomer conjugates**)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:657913 CAPLUS
DOCUMENT NUMBER: 137:196046
TITLE: Methods of treating diabetes mellitus with orally administered insulin oligomers
INVENTOR(S): Ekwuribe, Nnochiri N.; Price, Christopher H.; Still, James Gordon; Filbey, Jennifer Ann
PATENT ASSIGNEE(S): Nobex Corporation, USA; Radhakrishnan, Balasingam; Ansari, Aslam M.; Odenbaugh, Amy L.
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002065985	A2	20020829	WO 2002-US4440	20020214
WO 2002065985	A3	20040219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003050228	A1	20030313	US 2002-75097	20020213
EP 1409006	A2	20040421	EP 2002-709541	20020214

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:	US 2001-269198P	P	20010215
	US 2002-347713P	P	20020111
	WO 2002-US4440	W	20020214

AB Methods of treating diabetes mellitus using an effective amount of an oral insulin derivative are claimed. The structure of the insulin derivative is: insulin polypeptide-B-Lj-Gk-R-G'm-R'-G"n-T wherein: B is a bonding moiety; L is a linker moiety; G, G' and G" are individually selected spacer moieties; R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety; T is a terminating moiety; and j, k, m and n are individually 0 or 1. The structure of the insulin derivative is: insulin polypeptide-X(CH2)mY(C2H4O)nR, insulin polypeptide-X(CH2)m(OC2H4)nOR, or insulin polypeptide-NH-CO-(CH2)m(OC2H4)nOR, wherein: X and Y are ester moieties, thioester moieties, ether moieties, carbamate moieties, thiocarbamate moieties, carbonate moieties, thiocarbonate moieties, amide moieties, urea moieties or covalent bonds; m is between 1 and 24; n is between 1 and 50; and R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alc. moiety, or a fatty acid moiety. A specifically claimed derivative is insulin polypeptide-NH-CO-(CH2)5(OC2H4)7OCH3. Formulations for capsules are exemplified.

IC ICM A61K

CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 63

ST diabetes mellitus treatment oral **insulin oligomer conjugate**

IT 9004-10-8D, **Insulin**, oligomeric **conjugates**
452310-88-2D, oligomeric **conjugates** 452310-92-8D, oligomeric **conjugates** 452311-02-3D, oligomeric **conjugates**
452311-09-0D, oligomeric **conjugates** 452311-17-0D, oligomeric **conjugates** 452311-24-9D, oligomeric **conjugates**
452311-25-0D, oligomeric **conjugates** 452311-26-1D, oligomeric **conjugates** 452311-27-2D, oligomeric **conjugates**
452311-28-3D, oligomeric **conjugates** 452311-29-4D, oligomeric **conjugates** 452311-30-7D, oligomeric **conjugates**
452311-31-8D, oligomeric **conjugates** 452311-32-9D, oligomeric **conjugates** 452311-33-0D, oligomeric **conjugates**
452311-34-1D, oligomeric **conjugates** 452311-35-2D, oligomeric **conjugates** 452311-36-3D, oligomeric **conjugates**
452311-37-4D, oligomeric **conjugates** 452311-38-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of treating diabetes mellitus with orally administered **insulin oligomers**)

L24 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2000:911065 CAPLUS
DOCUMENT NUMBER:	134:76386
TITLE:	Amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components and methods for making and using the same
INVENTOR(S):	Ekwuribe, Nnochiri; Ramaswamy, Muthukumar; Rajagopalan, Jayanthi
PATENT ASSIGNEE(S):	Protein Delivery, Inc., USA
SOURCE:	PCT Int. Appl., 69 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078302	A1	20001228	WO 2000-US16879	20000619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6309633	B1	20011030	US 1999-336548	19990619
BR 2000011772	A	20020402	BR 2000-11772	20000619
EP 1196157	A1	20020417	EP 2000-942956	20000619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003502364	T2	20030121	JP 2001-504366	20000619
ZA 2001010099	A	20030307	ZA 2001-10099	20011207
NO 2001006143	A	20020218	NO 2001-6143	20011217

PRIORITY APPLN. INFO.:
US 1999-336548 A 19990619
WO 2000-US16879 W 20000619

AB The present invention relates generally to hydrolyzable drug-oligomer conjugates, pharmaceutical compns. comprising such conjugates, and to methods for making and using such conjugates and pharmaceutical compns. For example, a conjugate of insulin, PEG, and oleic acid was prepared and can be orally administered.

IC ICM A61K031-075
ICS A61K031-13; A61K031-16; A61K031-21; A61K031-325; A61K038-02; A61K038-28

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2

ST peptide drug **PEG** conjugate hydrolyzable

IT Proteins, specific or class
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Pituitary adenyl cyclase-activating; amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Drug delivery systems
Lipophilicity
(amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Antigens
Blood-coagulation factors
Bone morphogenetic proteins
Chemokines
Ciliary neurotrophic factor
Cytokines
Enkephalins
Gonadotropins
Growth factors, animal
Interferons
Interleukins
Neurotrophic factors

Peptides, biological studies
Platelet-derived growth factors
Tumor necrosis factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT **Polyoxyalkylenes**, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Neurotrophic factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(brain-derived; amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Drug delivery systems
(emulsions; amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Neurotrophic factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glial-derived; amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Proteins, specific or class
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis stimulating peptide; amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Thymus hormones
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thymostimulin; amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT Transforming growth factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-; amphiphilic drug- **oligomer** conjugates with hydrolyzable lipophile components)

IT Transforming growth factors
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-; amphiphilic drug- **oligomer** conjugates with hydrolyzable lipophile components)

IT 50-56-6, Oxytocin, biological studies 58-82-2, Bradykinin 69-25-0, Eledoisin 1066-17-7, Colistin 1393-25-5, Secretin 1404-26-8, Polymyxin b 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1407-47-2, Angiotensin 1947-37-1, Tetragastrin 5534-95-2, Pentagastrin 8049-47-6, Pancreatin 9001-01-8, Kallikrein 9001-25-6, Blood-coagulation factor VII 9001-27-8, Factor VIII 9001-28-9, Factor IX 9002-07-7, Trypsin 9002-60-2, Adrenocorticotrophin, biological studies 9002-61-3, Human chorionic gonadotropin 9002-61-3D, Human chorionic gonadotropin, β-chain 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-67-9, LH 9002-69-1, Relaxin 9002-71-5, TSH 9002-76-0, Gastrin 9002-79-3, MSH 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9011-97-6, Cholecystokinin 9013-66-5, Glutathione peroxidase 9014-42-0, Thrombopoietin 9015-68-3, Asparaginase 9015-71-8, Corticotropin-releasing factor 9015-94-5, Renin, biological studies 9034-39-3, Somatoliberin 9034-40-6, Luliberin 9038-70-4, Somatomedin

9039-53-6, Urokinase 9054-89-1, Superoxide dismutase 9061-61-4, Nerve growth factor 9063-57-4, Taftsin 9066-59-5, Lysozyme chloride 11000-17-2, Vasopressin 11062-77-4, Superoxide 11085-36-2, Human placental lactogen 11096-26-7, Erythropoietin 11128-99-7, Angiotensin II 12038-82-3 16679-58-6, Desmopressin 17650-98-5, Caerulein 24305-27-9, TRH 25126-32-3, Cholecystokinin-8 (swine) 33507-63-0, Substance P 37221-79-7, Vasoactive intestinal peptide 37231-28-0, Melittin 39379-15-2, Neurotensin 51110-01-1D, Somatostatin, derivs. 52906-92-0, Motilin 53678-77-6, Muramyldipeptide 59392-49-3, Gastric inhibitory peptide 60118-07-2, Endorphin 60529-76-2, Thymopoietin 61512-21-8, Thymosin 61912-98-9, **Insulin**-like growth factor 62229-50-9, Epidermal growth factor 62683-29-8, CSF 63340-72-7, Thymic humoral factor 67763-96-6, **Insulin**-like growth factor I 67763-97-7, **Insulin**-like growth factor II 70904-56-2, Kyotorphin 74913-18-1, Dynorphin 78922-62-0, Serum thymic factor 80043-53-4, Gastrin-releasing peptide 81627-83-0, MCSF 82785-45-3, Neuropeptide Y 83652-28-2, Calcitonin gene related peptide 83869-56-1, GM-CSF 85637-73-6, Atrial natriuretic peptide 103370-86-1, PTH-related protein 105250-86-0, Ebiratide 106096-92-8, Acidic fibroblast growth factor 106096-93-9, Basic fibroblast growth factor 106388-42-5, Peptide YY 116243-73-3, Endothelin 117148-67-1, Pancreastatin 119418-04-1, Galanin 130939-66-1, NT-3 143011-72-7, GCSF 143375-33-1, Neurotrophin 4
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amphiphilic drug-**oligomer conjugates** with hydrolyzable lipophile components)

IT 112-27-6, Triethylene glycol 112-77-6, Oleoyl chloride 7693-46-1, p-Nitrophenyl chloroformate 9004-10-8, **Insulin**, reactions 25322-68-3, **Peg**
RL: RCT (Reactant); RACT (Reactant or reagent)
(amphiphilic drug-**oligomer conjugates** with hydrolyzable lipophile components)

IT 9004-81-3P, Polyethylene glycollaurate 9004-96-0P, **Polyethylene glycol** oleate 10233-14-4P, Triethylene glycol oleate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(amphiphilic drug-**oligomer** conjugates with hydrolyzable lipophile components)

IT 112-27-6DP, Triethylene glycol, derivs., **conjugates** with **insulin** 7535-00-4DP, Galactosamine, **conjugates** with **PEG insulin 9004-10-8DP**, **Insulin**, **conjugates** with **PEG** derivs., biological studies 9004-81-3DP, Polyethylene glycollaurate, **conjugates** with **insulin** 9004-96-0DP, **Polyethylene glycol** oleate, **conjugates** with **insulin** 10233-14-4DP, Triethylene glycol oleate, **conjugates** with **insulin** 28397-10-6DP, Octanoic acid, 2-[2-(2-hydroxyethoxy)ethoxy]ethyl ester, **conjugates** with **insulin** 62304-85-2DP, Hexadecanoic acid, 2-[2-(2-hydroxyethoxy)ethoxy]ethyl ester, **conjugates** with **insulin**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amphiphilic drug-**oligomer conjugates** with hydrolyzable lipophile components)

IT **9004-10-8DP**, **Insulin**, **conjugates** with **PEG** derivs., biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amphiphilic drug-**oligomer conjugates** with

hydrolyzable lipophile components)
RN 9004-10-8 CAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:133428 CAPLUS
DOCUMENT NUMBER: 132:185416
TITLE: Blood-brain barrier therapeutics
INVENTOR(S): Ekwuribe, Nnochiri N.; Radhakrishnan, Balasingam; Price, Christopher H.; Anderson, Wesley R., Jr.; Ausari, Aslam M.
PATENT ASSIGNEE(S): Protein Delivery, Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009073	A2	20000224	WO 1999-US18248	19990812
WO 2000009073	A3	20000629		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6703381	B1	20040309	US 1998-134803	19980814
CA 2340418	AA	20000224	CA 1999-2340418	19990812
AU 9956726	A1	20000306	AU 1999-56726	19990812
AU 772494	B2	20040429		
EP 1105142	A2	20010613	EP 1999-943676	19990812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9914280	A	20011113	BR 1999-14280	19990812
JP 2002522463	T2	20020723	JP 2000-564577	19990812
US 2004102381	A1	20040527	US 2003-716578	20031119
US 2004110735	A1	20040610	US 2003-716975	20031119
PRIORITY APPLN. INFO.:			US 1998-134803 A	19980814
			WO 1999-US18248 W	19990812

AB The present invention relates to amphiphilic drug-oligomer conjugates capable of traversing the blood-brain barrier and to methods of making and using such conjugates. Amphiphilic drug-oligomer conjugates comprise a therapeutic compound conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled to a hydrophilic moiety. The conjugates of the invention further comprise therapeutic agents such as proteins, peptides, nucleosides, nucleotides, antiviral agents, antineoplastic agents, antibiotics, etc., and prodrugs, precursors, derivs. and intermediates thereof, chemical coupled to amphiphilic oligomers. One example conjugate prepared was Met-enkephalin with a succinimidyl triethylene glycol monohexadecyl ester derivative
IC ICM A61K

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 34
ST blood brain barrier conjugate peptide **oligomer**
IT Enkephalins
RL: RCT (Reactant); RACT (Reactant or reagent)
(analogs; blood-brain barrier therapeutics comprising drug-**oligomer** conjugates)
IT Blood-brain barrier
(blood-brain barrier therapeutics comprising drug-**oligomer** conjugates)
IT Antibodies
Blood-coagulation factors
CD4 (antigen)
Hemoglobins
Hypothalamic hormones
Interferons
Opioids
Peptides, biological studies
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer** conjugates)
IT **9004-10-8DP, Insulin, conjugates** with **polyoxyalkylene** derivative, biological studies 259229-23-7DP, conjugates with peptides
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)
IT 57-88-5, Cholesterol, reactions 111-46-6, reactions 112-27-6, Triethylene glycol 112-82-3 623-65-4, Palmitic anhydride 4484-59-7, Triethylene glycol monohexadecyl ether 6066-82-6, Hydroxysuccinimide 13887-98-4, 3,6,9-Trioxaundecanedioic acid 58569-55-4, Met-enkephalin 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-**oligomer** conjugates)
IT 5274-61-3P 31255-25-1P 62304-85-2P, Triethylene glycol monohexadecanoate 259228-98-3P 259228-99-4P 259229-23-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-**oligomer** conjugates)
IT 4484-59-7DP, conjugates with enkephalin 5274-61-3DP, conjugates with enkephalin 62304-85-2DP, conjugates with enkephalin 259229-00-0P 259229-01-1DP, conjugates with enkephalin 259229-02-2DP, conjugates with enkephalin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer** conjugates)
IT 50-56-6, Oxytocin, biological studies 74-79-3, Arginine, biological studies 1407-47-2, Angiotensin 9000-96-8, Arginase 9001-73-4, Papain 9001-78-9 9001-99-4, Ribonuclease 9002-07-7, Trypsin 9002-60-2, Adrenocorticotropic hormone, biological studies 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin 9004-07-3, Chymotrypsin 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9011-97-6, Cholecystokinin 9015-68-3, Asparaginase 9026-93-1,

Adenosine deaminase 9038-70-4, Somatomedin 9054-89-1, Superoxide dismutase 11000-17-2, Vasopressin 11096-26-7, Erythropoietin 17650-98-5, Caerulein 39379-15-2, Neurotensin 51110-01-1, Somatostatin 52906-92-0, Motilin 60118-07-2, Endorphin 74913-18-1, Dynorphin 80043-53-4, Gastrin-releasing peptide 82785-45-3, Neuropeptide Y 85916-47-8, Katacalcin (human) 139639-23-9, Tissue plasminogen activator 259229-03-3 259229-04-4 259229-05-5 259229-06-6 259229-07-7 259229-08-8
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer** conjugates)

IT **9004-10-8DP**, **Insulin**, **conjugates** with **polyoxyalkylene** derivative, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(blood-brain barrier therapeutics comprising drug-**oligomer conjugates**)

RN 9004-10-8 CAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L24 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:722184 CAPLUS
DOCUMENT NUMBER: 132:284007
TITLE: Oral **insulin** delivery: hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction
AUTHOR(S): Ekwuribe, N.; Ramaswamy, M.; Allaudeen, H. S.; Rajagopalan, J. S.; Radhakrishnan, B.; Davis, C. M.; Regina, D. C.
CORPORATE SOURCE: Protein Delivery Inc., Durham, NC, 27713, USA
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1999), 26th, 147-148
CODEN: PCRMEY; ISSN: 1022-0178
PUBLISHER: Controlled Release Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Insulin was chemical modified with hydrolyzable amphiphilic PEG derivative oligomers and they were formulated into microemulsions. Prolonged glucose reduction was observed following oral administration to dogs.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 2

ST **insulin conjugate PEG oligomer** oral delivery

IT **Polyoxyalkylenes**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fatty acyl esters and ethers, reaction products **insulin**, **oligomers**; hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction in oral **insulin** delivery)

IT Antidiabetic agents
(hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction in oral **insulin** delivery)

IT Drug delivery systems
(oral; hydrolyzable amphiphilic **oligomer conjugates**

prolong glucose reduction in oral **insulin** delivery)
IT **9004-10-8DP**, **Insulin**, reaction products with **PEG** derivative **oligomers**, biological studies 25322-68-3DP, **Peg**, fatty acyl esters and ethers, reaction products **insulin**, **oligomers**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction in oral **insulin** delivery)
IT **9004-10-8DP**, **Insulin**, reaction products with **PEG** derivative **oligomers**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrolyzable amphiphilic **oligomer conjugates** prolong glucose reduction in oral **insulin** delivery)
RN 9004-10-8 CAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:42265 CAPLUS
DOCUMENT NUMBER: 128:119653
TITLE: Methods and compositions for enhancing the bioadhesive properties of **polymers** using organic excipients
INVENTOR(S): Santos, Camilla A.; Jacob, Jules S.; Hertzog, Benjamin A.; Carino, Gerardo P.; Mathiowitz, Edith
PATENT ASSIGNEE(S): Brown University Research Foundation, USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9749385	A1	19971231	WO 1997-US10256	19970612
W: JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5955096	A	19990921	US 1996-670326	19960625
EP 912166	A1	19990506	EP 1997-929973	19970612
EP 912166	B1	20030115		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000513355	T2	20001010	JP 1998-503153	19970612
AT 230978	E	20030215	AT 1997-929973	19970612
PRIORITY APPLN. INFO.:			US 1996-670326 A	19960625
			WO 1997-US10256 W	19970612

AB Methods and compns. are provided for enhancing the bioadhesive properties of polymers used in drug delivery systems. The bioadhesive properties of a polymer are enhanced by incorporating an anhydride oligomer into the polymer to enhance the ability of the polymer to adhere to a tissue surface such as a mucosal membrane. Anhydride oligomers which enhance the bioadhesive properties of a polymer include oligomers synthesized from

dicarboxylic acid monomers, preferably those found in Krebs glycolysis cycle, especially fumaric acid. The oligomers can be incorporated within a wide range of polymers including proteins, polysaccharides and synthetic biocompatible polymers. In one embodiment, anhydride oligomers can be incorporated within polymers used to form or coat drug delivery systems, such as microspheres, which contain a drug or diagnostic agent. The oligomers can either be solubilized and blended with the polymers before manufacture or else used as a coating with polymers over existing systems. The polymers, for example in the form of microspheres, have improved ability to adhere to mucosal membranes, and thus can be used to deliver a drug or diagnostic agent via any of a range of mucosal membrane surfaces including those of the gastrointestinal, respiratory, excretory and reproductive tracts. Fumaric acid oligomer (mol. weight 240-280) 0.1 g and 0.2 g glycolide-lactide copolymer were dissolved in 10 mL methylene chloride and 0.022 g of micronized FeO was added to the polymer solution A Tris buffer solution containing Zn insulin 10 mg/mL was mixed with 10 % ZnSO4 solution to form crystals. The Zn insulin suspension then was added to the polymer solution and dispersed into petroleum ether. The nanospheres were collected and lyophilized. An in vitro release study of nanospheres loaded with 1.6 % insulin showed that 60 % of insulin was released within 2 h and that 95 % was released within 72 h.

IC ICM A61K009-16
ICS A61K009-51; A61K047-00; A61K047-30; A61K047-34; A61K047-12

CC 63-6 (Pharmaceuticals)

IT Adhesion, biological
Mucous membrane
(anhydride oligomers for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT Polyamides, biological studies
Polyanhydrides
Polycarbonates, biological studies
Polyesters, biological studies
Polyolefins
Polyoxyalkylenes, biological studies
Polyphosphazenes
Polysaccharides, biological studies
Polysiloxanes, biological studies
Polyurethanes, biological studies
Proteins, general, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anhydride oligomers for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT Imaging agents
(contrast, radiog.; anhydride oligomers for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT Drug delivery systems
(microspheres; anhydride oligomers for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT Drug delivery systems
(nanoparticles; anhydride oligomers for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT Vinyl compounds, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**polymers**; anhydride oligomers for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT 103-90-2, Acetaminophen 8049-62-5, Zinc **Insulin**

9004-10-8, **Insulin**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anhydride **oligomers** for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT 79-10-7D, 2-Propenoic acid, derivs., **polymers**, biological studies 79-41-4D, derivs., **polymers** 9003-05-8, Polyacrylamide 9003-16-1, Fumaric acid **polymer** 9004-34-6, Cellulose, biological studies 24980-41-4, Polycaprolactone 25248-42-4, Polycaprolactone 26776-29-4, Sebacic acid **polymer** 26780-50-7, Glycolide-lactide copolymer 117381-39-2, Fumaric acid-sebacic acid copolymer
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anhydride oligomers for enhancing bioadhesive properties of **polymers** in drug delivery systems)

IT **9004-10-8**, **Insulin**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anhydride **oligomers** for enhancing bioadhesive properties of **polymers** in drug delivery systems)

RN 9004-10-8 CAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L24 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:460087 CAPLUS
DOCUMENT NUMBER: 115:60087
TITLE: Simulation of isotopic peak patterns for high-mass oligomers and polynuclidic transition metal salts
AUTHOR(S): Pulfer, James D.; Derrick, Peter J.
CORPORATE SOURCE: Dep. Chem., Univ. Papua New Guinea, Waigani, Papua New Guinea
SOURCE: Australian Journal of Chemistry (1991), 44(6), 799-807
CODEN: AJCHAS; ISSN: 0004-9425
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An algorithm has been developed for rapidly and accurately simulating isotopic peak patterns of such diverse substances as mid- to high-mass-range peptides, e.g. bovine insulin (C254H377N65O75S6) and RNase (C587H909N171O197S12), large polymerized hydrocarbons, such as the styrene oligomer (C804H810), and polynuclidic transition metal salts, such as cesium tetrathiotungstate(VI) (Cs2WS4). The program requires less than 4 kb of random access memory; it is rapid, and not restricted by the size of the mol. ion. To calculate the exptl. observed peaks of bovine insulin within 2% error required 30 s on an IBM PC-XT 286 microcomputer fitted with a math coprocessor; similarly, all peaks of the styrene oligomer took 68 s on a Commodore 10-II personal computer. A fully documented, highly compact, version of the algorithm is available in either Fortran-77 or GW-Basic.

CC 73-8 (Optical, Electron, and Mass Spectroscopy and Other Related Properties)
Section cross-reference(s): 6, 7, 9, 22, 34, 36, 65, 78

ST isotopic peak pattern **oligomer** algorithm; **insulin** isotopic peak pattern algorithm; RNase isotopic peak pattern algorithm; styrene **oligomer** isotopic peak pattern; polynuclidic transition metal salt isotopic peak; mass spectra **oligomer** polynuclidic

metal salt
IT **Polymers**, properties
RL: PRP (Properties)
(oligomers, high-mass, simulation of isotopic peak patterns of, algorithm for)

L24 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:637745 CAPLUS
DOCUMENT NUMBER: 113:237745
TITLE: Lactic acid oligomer microspheres containing hydrophilic drugs
AUTHOR(S): Wada, R.; Hyon, S. H.; Ikada, Y.
CORPORATE SOURCE: Res. Cent. Med. Polym. Biomater., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Journal of Pharmaceutical Sciences (1990), 79(10), 919-24
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new method was developed for preparation of biodegradable lactic acid oligomer microspheres containing hydrophilic drugs. The microspheres were obtained by removal of solvent from an oil-in-oil emulsion through evaporation The solvent used for the dispersed phase solution was an MeCN-H2O mixture, while the continuous phase medium was cottonseed oil. Doxorubicin-HCl and insulin were successfully entrapped in the microspheres with high trapping efficiencies of 80 to 90%, and their release profiles were not accompanied with the burst effect. The release rate of the drugs from the microspheres was greatly affected by the initial loading of the drugs and the mol. weight of the lactic acid oligomer.
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Blood sugar
(**insulin** from microspheres containing lactic acid **oligomers** effect on, in diabetes)
IT **Polymer** degradation
(biochem., of lactic acid oligomer microspheres, drug release in relation to)
IT 9004-10-8, **Insulin**, biological studies
RL: BIOL (Biological study)
(microspheres of lactic acid **oligomers** containing, drug activity and release from)

=> □

=> d que nos
L1 985 SEA FILE=REGISTRY ABB=ON PLU=ON PS/FS AND C2H4O
L3 17 SEA FILE=REGISTRY ABB=ON PLU=ON L1 AND SQL=30
L4 15 SEA FILE=REGISTRY ABB=ON PLU=ON L1 AND SQL=21
L5 5 SEA FILE=REGISTRY ABB=ON PLU=ON L1 AND L3 AND L4
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON INSULIN/CN
L9 3 SEA FILE=CAPLUS ABB=ON PLU=ON L5
L14 46 SEA FILE=CAPLUS ABB=ON PLU=ON INSULIN/OBI (L) OLIGOMER#/OBI
L16 19 SEA FILE=CAPLUS ABB=ON PLU=ON L14 (L) CONJUG?/OBI
L17 1268292 SEA FILE=CAPLUS ABB=ON PLU=ON PEG/OBI OR POLYETHYLENE GLYCOL/OBI OR POLYMER##/OBI OR POLYOXYALKYLENE?/OBI
L18 13 SEA FILE=CAPLUS ABB=ON PLU=ON L14 AND L17
L19 483 SEA FILE=CAPLUS ABB=ON PLU=ON L8 (L) L17
L20 6 SEA FILE=CAPLUS ABB=ON PLU=ON L19 (L) OLIGOMER?/OBI
L21 42 SEA FILE=CAPLUS ABB=ON PLU=ON L19 (L) CONJUG?/OBI

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L22           4 SEA FILE=CAPLUS ABB=ON  PLU=ON  L21 AND OLIGOMER?/OBI
L23          13 SEA FILE=CAPLUS ABB=ON  PLU=ON  L20 OR L22 OR L18
L24          23 SEA FILE=CAPLUS ABB=ON  PLU=ON  L16 OR L23
L25        1407 SEA FILE=CAPLUS ABB=ON  PLU=ON  ALKYLENE GLYCOL#/OBI
L27           6 SEA FILE=CAPLUS ABB=ON  PLU=ON  L25 AND (INSULIN/OBI OR L8)
L28           4 SEA FILE=CAPLUS ABB=ON  PLU=ON  L27 NOT (L9 OR L24)

=> d .ca l28 1-4

L28  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2002:502742  CAPLUS
DOCUMENT NUMBER:          137:68166
TITLE:                    High viscosity non-polymeric liquid controlled
                          delivery system and medical or surgical device
INVENTOR(S):              Gibson, John W.; Sullivan, Stacey A.; Middleton, John
                          C.; Tipton, Arthur J.
PATENT ASSIGNEE(S):       Southern Biosystems, Inc., USA
SOURCE:                   U.S., 22 pp., Cont.-in-part of U.S. 5,968,542.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   5
PATENT INFORMATION:

     PATENT NO.            KIND   DATE        APPLICATION NO.          DATE
     ----------------      ----   --------    ---------------------    --------
     US 6413536             B1    20020702    US 1999-385107           19990827
     US 5747058             A     19980505    US 1995-474337           19950607
     WO 2001015734          A2    20010308    WO 2000-US23270          20000824
     WO 2001015734          A3    20010913
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
             CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     EP 1212092             A2    20020612    EP 2000-961358           20000824
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL
     JP 2003508449          T2    20030304    JP 2001-520145           20000824
     US 2004101557          A1    20040527    US 2002-316441           20021210
PRIORITY APPLN. INFO.:                         US 1995-474337      A2 19950607
                                               US 1995-478450      B2 19950607
                                               US 1997-944022      A2 19970915
                                               US 1999-385107      A  19990827
                                               WO 2000-US23270     W  20000824
                                               US 2000-699002      A2 20001026
OTHER SOURCE(S):          MARPAT 137:68166
AB   The present invention relates to novel nonpolymeric compds. and compns.
     that form liquid, high viscosity materials suitable for the delivery of
     biol. active substances in a controlled fashion, and for use as medical or
     surgical devices.  The materials can optionally be diluted with a solvent to
     form a material of lower viscosity, rendering the material easy to
     administer.  This solvent may be water insol. or water soluble, where the
     water soluble solvent rapidly diffuses or migrates away from the material in
     vivo, leaving a higher viscosity liquid material.  For example, a high
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viscosity liquid carrier was prepared by reacting 247.13 g (1.71 mol) DL-lactide, 62.87 g (0.54 mol) glycolide, and 49.6 g (0.42 mol) 1,6-hexanediol. Following initial melting, 1.84 mL (260 μmol) of a 0.141 M stannous 2-ethylhexanoate solution in toluene was added. The resulting product had an inherent viscosity of 0.058 dL/g in CHCl3 at 30°. The material was a liquid at room temperature

IC ICM A61F002-02
ICS A61F013-02; A61K009-14; B32B005-16; B01J013-02
NCL 424423000
CC 63-6 (Pharmaceuticals)
IT 51-21-8, 5-Fluorouracil 64-17-5, Ethanol, biological studies 67-64-1, Acetone, biological studies 67-66-3, Chloroform, biological studies 67-68-5, Dimethyl sulfoxide, biological studies 74-98-6, Propane, biological studies 75-43-4, Dichlorofluoromethane 75-69-4, Trichlorofluoromethane 77-93-0, Triethyl citrate 78-93-3, Methyl ethyl ketone, biological studies 79-20-9, Methyl acetate 97-64-3, Ethyl lactate 100-51-6, Benzyl alcohol, biological studies 100-79-8, 2,2-Dimethyl-1,3-dioxolane-4-methanol 102-76-1, Triacetin 105-60-2, Caprolactam, biological studies 106-97-8, Butane, biological studies 109-99-9, Tetrahydrofuran, biological studies 110-27-0, Isopropyl myristate 111-62-6, Ethyl oleate 111-90-0, Diethylene glycol monoethyl ether 112-80-1, Oleic acid, biological studies 115-10-6, Dimethyl ether 120-51-4, Benzyl benzoate 124-07-2D, Caprylic acid, esters with **alkylene glycols** 126-13-6, SAIB 141-78-6, Ethyl acetate, biological studies 334-48-5D, Capric acid, esters with **alkylene glycols** 431-89-0, 1,1,1,2,3,3,3-Heptafluoropropane 616-45-5, 2-Pyrrolidone 811-97-2, R 134a 872-50-4, N-Methyl-2-pyrrolidone, biological studies 3079-28-5, Decyl methyl sulfoxide 7481-89-2, Dideoxycytidine 9001-63-2, Lysozyme 9002-72-6, Growth hormone **9004-10-8**, **Insulin**, biological studies 11096-26-7, Erythropoietin 25265-75-2, Butylene glycol 25322-68-3, Polyethylene glycol 30516-87-1, Zidovudine 31692-85-0, Glycofurol 34424-98-1, Caprol 10G40 38396-39-3, Bupivacaine 52814-38-7, Tetraglycol 59227-89-3, 1-Dodecylazacycloheptan-2-one 62031-54-3, Fibroblast growth factor 76009-37-5, Caprol 6G20 143011-72-7, Granulocyte colony stimulating factor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high viscosity ester liquid carriers for controlled-release drug delivery systems)
REFERENCE COUNT: 129 THERE ARE 129 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:167840 CAPLUS
DOCUMENT NUMBER: 134:227367
TITLE: High viscosity liquid controlled delivery system and medical or surgical device
INVENTOR(S): Gibson, John W.; Sullivan, Stacey A.; Middleton, John G.; Tipton, Arthur J.
PATENT ASSIGNEE(S): Southern Biosystems, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001015734	A2	20010308	WO 2000-US23270	20000824
WO 2001015734	A3	20010913		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6413536	B1	20020702	US 1999-385107	19990827
EP 1212092	A2	20020612	EP 2000-961358	20000824
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003508449	T2	20030304	JP 2001-520145	20000824
PRIORITY APPLN. INFO.:			US 1999-385107	A 19990827
			US 1995-474337	A2 19950607
			US 1995-478450	B2 19950607
			US 1997-944022	A2 19970915
			WO 2000-US23270	W 20000824

OTHER SOURCE(S): MARPAT 134:227367

AB The present invention relates to novel nonpolymeric compds. and compns. that form liquid, high viscosity materials suitable for the delivery of biol. active substances in a controlled fashion, and for use as medical or surgical devices. The materials can optionally be diluted with a solvent to form a material of lower viscosity, rendering the material easy to administer. This solvent may be water insol. or water soluble, where the water soluble solvent rapidly diffuses or migrates away from the material in vivo, leaving a higher viscosity liquid material. A compound 1,6-hexanediol lactate s-hydroxycaproic acid was prepared and dissolved in N-methylpyrrolidone at a weight ratio of 70:30, and then 10 % bupivacaine base was added to this mixture and dissolved. Drops weighing approx. 100 mg were precipitated into 40 mL buffer. Samples of buffer were removed at specified times and replaced with fresh buffer. Buffer samples were analyzed by UV-vis spectrophotometry at 265 nm to determine the concentration of bupivacaine in each buffer sample.

IC ICM A61K047-14
ICS A61K009-70; A61K009-12

CC 63-6 (Pharmaceuticals)

IT **9004-10-8**, **Insulin**, biological studies 11096-26-7, Erythropoietin 12629-01-5, Human growth hormone 62031-54-3, Fibroblast growth factor 66419-50-9, Bovine somatotropin 143011-72-7, Granulocyte colony stimulating factor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(active ingredients; high viscosity liquid compns. containing nonpolymeric esters for controlled delivery system and medical or surgical device)

IT 64-17-5, Ethanol, biological studies 67-64-1, Acetone, biological studies 67-68-5, Dimethyl sulfoxide, biological studies 74-98-6, Propane, biological studies 75-43-4, Dichlorofluoromethane 75-69-4, Trichlorofluoromethane 77-93-0, Triethyl citrate 78-93-3, Methyl ethyl ketone, biological studies 79-20-9, Methyl acetate 97-64-3, Ethyl lactate 100-51-6, Benzyl alcohol, biological studies 100-79-8, 2,2-Dimethyl-1,3-dioxolane-4-methanol 102-76-1, Triacetin 105-60-2, Caprolactam, biological studies 106-97-8, Butane, biological studies 109-99-9, Tetrahydrofuran, biological studies 110-27-0, Isopropyl myristate 111-62-6, Ethyl oleate 111-90-0, Diethylene glycol monoethyl

ether 112-80-1, Oleic acid, biological studies 115-10-6, Dimethyl ether 120-51-4, Benzyl benzoate 124-07-2D, Caprylic acid, esters with glycerol or **alkylene glycols** 141-78-6, Ethyl acetate, biological studies 334-48-5D, Capric acid, esters with glycerol or **alkylene glycols** 616-45-5, 2-Pyrrolidone 872-50-4, N-Methyl-2-pyrrolidone, biological studies 3079-28-5, Decylmethylsulfoxide 6336-49-8 25265-75-2, Butylene glycol 25322-68-3, Polyethylene glycol 29759-38-4, Tetrafluoroethane 31692-85-0, Glycofurol 59227-89-3, 1-Dodecylazacycloheptan-2-one
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvent; high viscosity liquid compns. containing nonpolymeric esters for controlled delivery system and medical or surgical device)

L28 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:249067 CAPLUS
DOCUMENT NUMBER: 130:276757
TITLE: Use of nordihydroguaiaretic acid to lower serum triglycerides, blood pressure and to treat syndrome X
INVENTOR(S): Reaven, Gerald M.; Balwani, Gul P.; Scribner, Karen A.; Reed, Michael J.
PATENT ASSIGNEE(S): Shaman Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9917761	A1	19990415	WO 1998-US15594	19980731
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9887592	A1	19990427	AU 1998-87592	19980731
PRIORITY APPLN. INFO.:			US 1997-944848	19971006
			WO 1998-US15594	19980731

AB The invention is directed to formulations comprising nordihydroguaiaretic acid (NDGA) and an amphiphilic vehicle. The invention is also directed to pharmaceutical compns. comprising a formulation of the present invention and a pharmaceutically acceptable carrier. The invention further provides methods for using NDGA, including but not limited to, the NDGA containing formulations and compns. of the invention as agents to lower serum triglyceride, free fatty acid or glycerol level in animals. NDGA containing formulations and compns. can also be used as agents to lower free fatty acid levels in animals that have normal levels of glucose, triglycerides and cholesterol. The NDGA formulations can be used to lower blood pressure. The methods of the present invention can also be used to treat or ameliorate the characteristic manifestations of Syndrome X in a non-diabetic animal with normal serum glucose levels. This includes lowering of one or more of the following: serum insulin level, blood pressure, serum triglycerides and free fatty acid levels. The methods entail administering, to an animal in need of such treatment, an effective amount of a composition whose active ingredient consists essentially of NDGA. The invention is also directed to methods of treatment using NDGA in conjunction with another hypolipidemic agent.

IC ICM A61K031-05
ICS A61K009-107; A61K047-14
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
ST nordihydroguaiaretic acid hypolipidemic hypotensive; syndrome X treatment nordihydroguaiaretic acid; **insulin** lowering nordihydroguaiaretic acid
IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(esters, (poly)**alkylene glycol** esters;
nordihydroguaiaretic acid to lower serum triglycerides, blood pressure and to treat syndrome X)
IT Diabetes mellitus
(non-**insulin**-dependent; nordihydroguaiaretic acid to lower serum triglycerides, blood pressure and to treat syndrome X)
IT 50-99-7, D-Glucose, biological studies 56-81-5, 1,2,3-Propanetriol, biological studies **9004-10-8**, **Insulin**, biological studies 9005-79-2, Glycogen, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nordihydroguaiaretic acid to lower serum triglycerides, blood pressure and to treat syndrome X)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:682099 CAPLUS
DOCUMENT NUMBER: 129:293900
TITLE: Oral delivery of proteins by hydrogel matrixes comprising a crosslinked copolymer of methacrylic acid and poly(**alkylene glycol**)monomethacrylate
INVENTOR(S): Peppas, Nicholas A.; Lowman, Anthony M.; Nagai, Tsuneji; Morishita, Mariko
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843615	A1	19981008	WO 1998-US6563	19980402
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9868809	A1	19981022	AU 1998-68809	19980402
AU 727053	B2	20001130		
EP 975328	A1	20000202	EP 1998-914454	19980402
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
TR 9903240	T2	20000522	TR 1999-9903240	19980402
NZ 500075	A	20010330	NZ 1998-500075	19980402

BR 9808466	A	20010807	BR 1998-8466		19980402
JP 2002512607	T2	20020423	JP 1998-542015		19980402
NO 9904757	A	19991129	NO 1999-4757		19990930
MX 9909031	A	20000228	MX 1999-9031		19991001
PRIORITY APPLN. INFO.:			US 1997-42280P	P	19970402
			US 1997-61367P	P	19971008
			WO 1998-US6563	W	19980402

AB A composition and method are described for the oral administration of bioactive components to vertebrates. The method comprises the step of orally administering the vertebrate a composition comprising a swellable hydrogel matrix and a bioactive composition contained within the hydrogel matrix. Poly(methacrylic acid-ethylene glycol) hydrogels were prepared at 37° by free-radical solution polymerization of methacrylic acid and PEG monomethacrylate, the oligomer chains were then crosslinked with tetraethylene glycol dimethacrylate crosslinked copolymer of methacrylic acid and poly(alkylene glycol)monomethacrylate. The ensuing hydrogels were rinsed for a week in water to remove unreacted monomer and non-crosslinked oligomer chains, then dried and ground into a powder having an average particulate diameter ranging from 100-150 μm. A solution of insulin in phosphate buffer, pH = 7.4, was prepared and above hydrogel was added to the solution to load the hydrogels by equilibrium partitioning. The hydrogel matrix was then contacted with an acid solution to introduce the formation of interpolymer complexes, and thus reduce the pore size of hydrogel matrix. The hydrogel microspheres were then collected by filtration, and dried. The mean insulin incorporation efficiency into the hydrogel matrix reached 94% at 30 min after the experiment Less than 10% of the insulin was released from the polymer in pH = 1.3, but after the microspheres were placed in pH = 7.4 buffer solution, the hydrogels swelled rapidly allowing for a rapid release of insulin, showing the graft copolymer was useful for development of oral insulin delivery system.

IC ICM A61K009-10
ICS A61K009-66; A61K047-34

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 38

IT Drug delivery systems
(hydrogels; oral delivery of proteins by hydrogel matrixes comprising crosslinked copolymer of methacrylic acid and poly(**alkylene glycol**)monomethacrylate)

IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral delivery of proteins by hydrogel matrixes comprising crosslinked copolymer of methacrylic acid and poly(**alkylene glycol**)monomethacrylate)

IT Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral delivery of proteins by hydrogel matrixes comprising crosslinked copolymer of methacrylic acid and poly(**alkylene glycol**)monomethacrylate)

IT 173283-58-4P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral delivery of proteins by hydrogel matrixes comprising crosslinked copolymer of methacrylic acid and poly(**alkylene glycol**)monomethacrylate)

IT 58-55-9, Theophylline, biological studies 1404-90-6, Vancomycin **9004-10-8**, **Insulin**, biological studies 37205-61-1, Protease inhibitor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral delivery of proteins by hydrogel matrixes comprising crosslinked

copolymer of methacrylic acid and poly(**alkylene glycol**)monomethacrylate)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> fil medline biosis
FILE 'MEDLINE' ENTERED AT 14:09:08 ON 05 AUG 2004

FILE 'BIOSIS' ENTERED AT 14:09:08 ON 05 AUG 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

=> d que l7
L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON INSULIN/CN
L2 411635 SEA L1 OR INSULIN
L3 35757 SEA POLYETHYLENE GLYCOL OR ALKYLENE GLYCOL
L4 552 SEA L2 AND L3
L6 28 SEA L4 AND CONJUG?
L7 23 DUP REM L6 (5 DUPLICATES REMOVED)

=> d bib ab 1-23

L7 ANSWER 1 OF 23 MEDLINE on STN
AN 2003598169 MEDLINE
DN PubMed ID: 14679073
TI Development and validation of radioligand binding assays to measure total, IgA, IgE, IgG, and IgM **insulin** antibodies in human serum.
AU Moxness MichaeI; Foley Jim; Stene Mark; Finco-Kent Deborah; Bedian Vahe; Krasner Alan; Kawabata Thomas
CS Esoterix Incorporated, Calabasas, California, USA.
SO Annals of the New York Academy of Sciences, (2003 Nov) 1005 265-8. Journal code: 7506858. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE) (VALIDATION STUDIES)
LA English
FS Priority Journals
EM 200401
ED Entered STN: 20031219
Last Updated on STN: 20040117
Entered Medline: 20040116
AB Radioligand binding assays for total and Ig classes of **insulin** antibodies (IAB) were developed and validated. For each assay, **insulin**-extracted serum samples were incubated with radiolabeled **insulin** in the presence and absence of high levels of unlabeled **insulin** to determine nonspecific binding and total binding, respectively. To measure total IAB, antibody-bound **insulin** was precipitated with a **polyethylene glycol** solution, washed, and counted in a gamma-counter. To measure IgG IAB, samples were treated with protein G-Sepharose beads, centrifuged, washed, and counted. For the measurement of IgA, IgE, and IgM IAB, IgG was removed from the samples and treated with anti-IgA, -IgE, or -IgM **conjugated** to Sepharose beads, centrifuged, washed, and counted. The acid/charcoal extraction of bound and unbound **insulin** from serum samples was optimized. Specificity and binding capacity of the protein G and antibody-bound beads were evaluated and optimized. The linear region of the total and IgG IAB assays was determined using serum samples containing

high levels of **insulin** antibodies. The limit of quantitation, limit of detection, and precision for all the assays were also determined.

L7 ANSWER 2 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:554136 BIOSIS
DN PREV200300551411
TI NON - VIRAL GENE TRANSFER TO THE RETINA OF MICE AND MONKEYS FOLLOWING INTRAVENOUS ADMINISTRATION.
AU Schlachetzki, F. [Reprint Author]; Zhang, Y. [Reprint Author]; Zhu, C. [Reprint Author]; Boado, R. [Reprint Author]; Pardridge, W. M. [Reprint Author]
CS Medicine, University of California Los Angeles, Los Angeles, CA, USA
SO ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 3599. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Nov 2003
Last Updated on STN: 26 Nov 2003
AB Purpose: The success of gene therapy is limited by the gene delivery system. A new approach to retina gene therapy enables the widespread expression of a therapeutic gene throughout the retina with intravenous non-viral gene transfer. Methods: The SV40 promoter expression plasmid encoding the exogenous gene, e.g., either luciferase or b-galactosidase, is encapsulated in the interior of pegylated immunoliposomes (PIL), which function as an artificial virus of about 85 nm in diameter. The PIL is targeted across the cellular barriers in the eye with a receptor-specific monoclonal antibody (MAb). The targeting MAb, which is **conjugated** to the tips of strands of **polyethylene glycol** projecting from the surface of the PIL, is directed at either the transferrin receptor (TfR) in mice or the **insulin** receptor (IR) in Rhesus monkey. Owing to expression of the TfR or IR on both the blood-retinal barrier and the plasma membrane of ocular cells, the PIL carrying the gene is delivered to the nuclear compartment of cells in the eye. Results: In mice, the b-galactosidase gene was expressed throughout the entire retina, with exception of the photoreceptor cells, following targeting with the TfRMAb-PIL. The reduced gene expression in the photoreceptor cells with the TfRMAb-PIL was correlated with minimal TfR expression in the outer nuclear layer (ONL). In contrast, diffuse gene expression in the photoreceptor cells and inner segments was observed in the primate retina following intravenous administration of the HIRMAb targeted PIL. Immunocytochemistry showed that the IR is expressed in the primate ONL (Fig.). Conclusions: This approach makes feasible adult transgenics in 24 hours, and enables the delivery of therapeutic genes throughout the entire retina without viral vectors or ocular injections. Fig.: beta-Galactosidase histochemistry of the monkey retina reveals widespread gene expression.

L7 ANSWER 3 OF 23 MEDLINE on STN
AN 2002291886 MEDLINE
DN PubMed ID: 11842083
TI The **insulin**-sensitive glucose transporter, GLUT4, interacts physically with Daxx. Two proteins with capacity to bind Ubc9 and **conjugated** to SUMO1.
AU Lalioti Vassiliki S; Vergarajauregui Silvia; Pulido Diego; Sandoval Ignacio V

CS Centro de Biologia Molecular Severo Ochoa, Consejo Superior de Investigaciones Cientificas, Universidad Autonoma de Madrid, Madrid 28049, Spain.
SO Journal of biological chemistry, (2002 May 31) 277 (22) 19783-91. Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020529
Last Updated on STN: 20030105
Entered Medline: 20020702
AB In this study we have used the yeast two-hybrid system to identify proteins that interact with the carboxyl-cytoplasmic domain (residues 464-509) of the **insulin**-sensitive glucose transporter GLUT4 (C-GLUT4). Using as bait C-GLUT4, we have isolated the carboxyl domain of Daxx (C-Daxx), the adaptor protein associated with the Fas and the type II TGF-beta (TbetaRII) receptors (1,2). The two-hybrid interaction between C-GLUT4 and C-Daxx is validated by the ability of in vitro translated C-GLUT4 to interact with in vitro translated full-length Daxx and C-Daxx. C-Daxx does not interact with the C-cytoplasmic domain of GLUT1, the ubiquitous glucose transporter homologous to GLUT4. Replacement of alanine and serine for the dileucine pair (Leu(489)-Leu(490)) critical for targeting GLUT4 from the trans-Golgi network to the perinuclear intracellular store as well as for its surface internalization by endocytosis inhibits 2-fold the interaction of C-GLUT4 with Daxx. Daxx is pulled down with GLUT4 immunoprecipitated from lysates of 3T3-L1 fibroblasts stably transfected with GLUT4 and 3T3-L1 adipocytes expressing physiological levels of the two proteins. Similarly, GLUT4 is recovered with anti-Daxx immunoprecipitates. Using an established cell fractionation procedure we present evidence for the existence of two distinct intracellular Daxx pools in the nucleus and low density microsomes. Confocal immunofluorescence microscopy studies localize Daxx to promyelocytic leukemia nuclear bodies and punctate cytoplasmic structures, often organized in strings and underneath the plasma membrane. Daxx and GLUT4 are SUMOlated as shown by their reaction with an anti-SUMO1 antibody and by the ability of this antibody to pull down Daxx and GLUT4.

L7 ANSWER 4 OF 23 MEDLINE on STN
AN 2002309799 MEDLINE
DN PubMed ID: 12052712
TI Effects of PEG **conjugation** on **insulin** properties.
AU Hinds Kenneth D; Kim Sung Wan
CS Department of Pharmaceutics and Pharmaceutical Chemistry/CCCD, University of Utah, 20 South 2030 East Rm. 201, Salt Lake City, UT 84112, USA.
NC DK-50557 (NIDDK)
SO Advanced drug delivery reviews, (2002 Jun 17) 54 (4) 505-30. Ref: 108 Journal code: 8710523. ISSN: 0169-409X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020611
Last Updated on STN: 20020813
Entered Medline: 20020812
AB The goal of this research was to determine whether the site-specific

attachment of poly(ethylene glycol) to **insulin** could enhance the physical and pharmacological properties of **insulin** without negatively affecting its biological activity or immunological properties. Electrophilically activated derivatives of low-molecular-weight monomethoxypoly(ethylene glycol) (mPEG) were chemically coupled to **insulin** via its amino groups at positions phenylalanine-B1 or lysine-B29, with an amide bond being formed between the polymer and protein. The site-specific attachment of mPEG to **insulin** did not substantially alter **insulin**'s secondary/tertiary structure, self-association behavior, or potency in vivo. However, mPEG attachment did significantly enhance **insulin**'s resistance to aggregation. In addition, the pegylation of **insulin** almost completely eliminates the resultant **conjugate**'s immunogenicity, allergenicity, and antigenicity. Finally, the **conjugates** were observed to remain in the systemic circulation for longer periods of time than unmodified **insulin** after subcutaneous administration.

L7 ANSWER 5 OF 23 MEDLINE on STN DUPLICATE 1
AN 2002411751 MEDLINE
DN PubMed ID: 12167225
TI Effect of cross-linked hemoglobin on functionality and viability of microencapsulated pancreatic islets.
AU Chae Su Young; Kim Sung Wan; Bae You Han
CS Center for Biomaterials and Biotechnology, Department of Materials Science and Engineering, Kwangju Institute of Science and Technology, Kwangju, South Korea.
NC DK 56884 (NIDDK)
SO Tissue engineering, (2002 Jul) 8 (3) 379-94.
Journal code: 9505538. ISSN: 1076-3279.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 20020809
Last Updated on STN: 20030206
Entered Medline: 20030205
AB Of many obstacles involved in developing a bioartificial pancreas, which consists of encapsulated and physically immunoprotected islets, for long-term implantation in **insulin**-dependent diabetic patients, the impaired functionality and decreasing viability of encapsulated islets over time are critical factors in determining the size and longevity of the implant. These factors are closely associated with short oxygen supply to the encaged islets from the implant site. To facilitate oxygen transport to islets in the capsules, we coencapsulated hemoglobin cross-linked with difunctional **polyethylene glycol** (Hb-**conjugate**, Hb-C) which is large in size (>100 kDa), thus preventing diffusional loss through the immunoprotecting membrane. The coencapsulation of Hb-C with islets in alginate-poly-L-lysine microcapsules by dissolving Hb-C in an islet-suspended alginate solution at a concentration of 0.25 mM improved the **insulin** secretion and viability of the islets. At week 0, the islets, coencapsulated with Hb-C, cultured at P(O2) = 40 mmHg (assumed oxygen partial pressure in the most common implant site, the peritoneal cavity), secreted 200% more **insulin** compared with the control islets without Hb-C at glucose concentrations of both 100 and 300 mg/dL. The Hb-C effect became more significant with time at higher glucose concentrations. After culturing the islets for 8 weeks at 40 mmHg, the **insulin** secretion was enhanced 200 and 550% at glucose concentrations of 100 and 300 mg/dL as compared with the control, respectively. The results were closely

associated with improved viability and suggest that the introduction of Hb-C is an effective approach to maintaining the oxygen supply to encapsulated islets. In addition, Hb-C coencapsulation with pancreatic islets may (1) provide a partial clue to reducing the large size of the biohybrid artificial pancreas, (2) lead to a reduced need for pancreas donation, and (3) prolong the longevity of the biohybrid artificial pancreas in the body.

L7 ANSWER 6 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:55538 BIOSIS
DN PREV200200055538
TI Synthesis of **insulin** derivatives.
AU Liu, Feng [Inventor]; Kim, Sung Wan [Inventor]; Baudys, Miroslav [Inventor, Reprint author]
CS Salt Lake City, UT, USA
ASSIGNEE: University of Utah Research Foundation
PI US 6323311 November 27, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 27, 2001) Vol. 1252, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 9 Jan 2002
Last Updated on STN: 25 Feb 2002
AB A method for the "one-pot" synthesis of **insulin** derivatives wherein **insulin** is modified at the alpha-amino group of the PheB1 residue is described. The method comprises protecting the alpha-amino group of the GlyA1 residue and the epsilon-amino group of the LysB29 residue by reaction of **insulin** with a cyclic anhydride of a dicarboxylic acid in the presence of a tertiary amine. The protected **insulin** is then reacted with an activated hydrophilic compound, preferably an activated **polyethylene glycol**, resulting in a **conjugate** of the hydrophilic compound coupled to the PheB1 residue of **insulin**. The protecting groups are then removed from the **conjugate** under mild acidic conditions, and the resulting **insulin** derivative can be purified by conventional methods. Monosubstituted **insulin** derivatives wherein **polyethylene glycol** or derivatives thereof or glycosides are coupled to the PheB1 residue of **insulin** are also described.

L7 ANSWER 7 OF 23 MEDLINE on STN DUPLICATE 2
AN 2001549488 MEDLINE
DN PubMed ID: 11595543
TI Clinical use of a growth hormone receptor antagonist in the treatment of acromegaly.
AU Drake W M; Parkinson C; Besser G M; Trainer P J
CS Department Endocrinology, St Bartholomew's Hospital, London, UK EC1A 7BE.
SO Trends in endocrinology and metabolism: TEM, (2001 Nov) 12 (9) 408-13.
Ref: 28
Journal code: 9001516. ISSN: 1043-2760.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011015
Last Updated on STN: 20030314
Entered Medline: 20011228

AB The elucidation of the mechanisms by which growth hormone (GH) interacts with its receptor has facilitated the design of compounds that function as GH-receptor antagonists. One such compound, B2036, has been **conjugated** to **polyethylene glycol** to produce a drug, pegvisomant, that has a powerful ability to lower circulating concentrations of **insulin**-like growth factor I (IGF-I), the principal mediator of GH action, in patients with acromegaly and to improve the symptoms and signs associated with GH excess. This article describes the mechanism of action of GH-receptor antagonists, reviews the preclinical and clinical data on the use of pegvisomant and discusses some of the challenges that lie ahead in judging the efficacy of a treatment that, unlike established therapies for acromegaly, does not aim to modify the underlying cause of acromegaly, namely excess GH secretion, but aims to lower serum IGF-I levels to normal.

L7 ANSWER 8 OF 23 MEDLINE on STN DUPLICATE 3
AN 2001232456 MEDLINE
DN PubMed ID: 11170367
TI New PEGs for peptide and protein modification, suitable for identification of the PEGylation site.
AU Veronese F M; Sacca B; Polverino de Laureto P; Sergi M; Caliceti P; Schiavon O; Orsolini P
CS Department of Pharmaceutical Sciences, University of Padova, Via Marzolo 5, 35131 Padova, Italy.. veronese@pdfar3.dsfarm.unipd.it
SO Bioconjugate chemistry, (2001 Jan-Feb) 12 (1) 62-70.
Journal code: 9010319. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503
AB New PEG derivatives were studied for peptide and protein modification, based upon an amino acid arm, Met-Nle or Met-beta Ala, activated as succinimidyl ester. PEG-Met-Nle-OSu or PEG-Met-beta Ala-OSu react with amino groups in protein-yielding **conjugates** with stable amide bond. From these **conjugates** PEG may be removed by BrCN treatment, leaving Nle or beta Ala as reporter amino acid, at the site where PEG was bound. The **conjugation** of PEG and its removal by BrCN treatment was assessed on a partial sequence of glucagone and on lysozyme as model peptide or protein. Furthermore, **insulin**, a protein with three potential sites of PEGylation, was modified by PEG-Met-Nle, and the PEG isomers were separated by HPLC. After removal of PEG, as reported above, the sites of PEGylation were identified by characterization of the two **insulin** chains obtained after reduction and carboxymethylation. Mass spectrometry, amino acid analysis and Edman sequence, could reveal the position of the reporter norleucine that corresponds to the position of PEG binding.

L7 ANSWER 9 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:357148 BIOSIS
DN PREV200100357148
TI Hypoglycemic activity of **polyethylene glycol-insulin conjugate.**
AU EL-Sayed, Mohamed M. [Reprint author]; Yacout, Galila A. [Reprint author]; Abaza, Mohamed S. [Reprint author]; El-Kersh, Mohamed A. [Reprint author]; Helmy, Hanna M. [Reprint author]
CS Department of Biochemistry, Faculty of Science, Alexandria University,

Alexandria, Egypt
SO Journal of the Medical Research Institute, (2001) Vol. 22, No. 1, pp. 46-52. print.
ISSN: 1110-0133.
DT Article
LA English
ED Entered STN: 2 Aug 2001
Last Updated on STN: 19 Feb 2002
AB The present study was undertaken to prepare a synthetic **polyethylene glycol-insulin conjugate** (PEG-**insulin**) and find out its effect on the alloxan-induced diabetic rats. The studied parameters including glucose levels, urea, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), protein and hexokinase activity, showed a significant improvement in case of diabetic rats treated with PEG-**insulin** **conjugate**, compared to those rats treated with **insulin** alone.

L7 ANSWER 10 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:236224 BIOSIS
DN PREV200000236224
TI Extending **insulin** action in vivo by **conjugation** to carboxymethyl dextran.
AU Baudys, M. [Reprint author]; Liu, F. [Reprint author]; Mix, D. [Reprint author]; Kim, S. W. [Reprint author]; Letourneur, D.; Josefonvicz, J.
CS Department of Pharmaceutics and Pharmaceutical Chemistry, Center for Controlled Chemical Delivery, University of Utah, Salt Lake City, UT, 84112, USA
SO Journal of Controlled Release, (Feb. 14, 2000) Vol. 64, No. 1-3, pp. 281-283. print.
Meeting Info.: Proceedings of the Fifth European Symposium on Controlled Drug Delivery. Noordwijk aan Zee, Netherlands. April 01-03, 1998.
CODEN: JCREEC. ISSN: 0168-3659.
DT Conference; (Meeting)
Conference; (Meeting Paper)
LA English
ED Entered STN: 7 Jun 2000
Last Updated on STN: 5 Jan 2002

L7 ANSWER 11 OF 23 MEDLINE on STN
AN 2000191518 MEDLINE
DN PubMed ID: 10725096
TI Synthesis and characterization of poly(ethylene glycol)-**insulin** **conjugates.**
AU Hinds K; Koh J J; Joss L; Liu F; Baudys M; Kim S W
CS Department of Pharmaceutics and Pharmaceutical Chemistry/Center for Controlled Chemical Delivery, University of Utah, Biomedical Polymers Research Building, Room 205, Salt Lake City, Utah 84112, USA.
NC DK50557 (NIDDK)
SO Bioconjugate chemistry, (2000 Mar-Apr) 11 (2) 195-201.
Journal code: 9010319. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000531
AB Human **insulin** was modified by covalent attachment of short-chain

(750 and 2000 Da) methoxypoly (ethylene glycol) (mPEG) to the amino groups of either residue PheB1 or LysB29, resulting in four distinct **conjugates**: mPEG(750)-PheB1-**insulin**, mPEG(2000)-PheB1-**insulin**, mPEG(750)-LysB29-**insulin**, and mPEG(2000)-LysB29-**insulin.** Characterization of the **conjugates** by MALDI-TOF mass spectrometry and N-terminal protein sequence analyses verified that only a single polymer chain (750 or 2000 Da) was attached to the selected residue of interest (PheB1 or LysB29). Equilibrium sedimentation experiments were performed using analytical ultracentrifugation to quantitatively determine the association state(s) of **insulin** derivatives. In the concentration range studied, all four of the **conjugates** and Zn-free **insulin** exist as stable dimers while Zn(2+)-**insulin** was exclusively hexameric and Lispro was monomeric. In addition, **insulin** (**conjugate**) self-association was evaluated by circular dichroism in the near-ultraviolet wavelength range (320-250 nm). This independent method qualitatively suggests that mPEG-**insulin conjugates** behave similarly to Zn-free **insulin** in the concentration range studied and complements results from ultracentrifugation studies. The physical stability/resistance to fibrillation of mPEG-**insulin conjugates** in aqueous solution were assessed. The data proves that mPEG(750 and 2000)-PheB1-**insulin conjugates** are substantially more stable than controls but the mPEG(750 and 2000)-LysB29-**insulin conjugates** were only slightly more stable than commercially available preparations. Circular dichroism studies done in the far ultraviolet region confirm **insulin**'s tertiary structure in aqueous solution is essentially conserved after mPEG **conjugation.** In vivo pharmacodynamic assays reveal that there is no loss in biological activity after **conjugation** of mPEG(750) to either position on the **insulin** B-chain. However, attachment of mPEG(2000) decreased the bioactivity of the **conjugates** to about 85% of Lilly's HumulinR formulation. The characterization presented in this paper provides strong testimony to the fact that attachment of mPEG to specific amino acid residues of **insulin**'s B-chain improves the **conjugates**' physical stability without appreciable perturbations to its tertiary structure, self-association behavior, or in vivo biological activity.

L7 ANSWER 12 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:147595 BIOSIS
DN PREV199900147595
TI Site-specific **insulin conjugates** with enhanced stability and extended action profile.
AU Uchio, Takashi; Baudys, Miroslav; Liu, Feng; Song, Soo Chang; Kim, Sung Wan [Reprint author]
CS Dep. Pharmaceutics Pharmaceutical Chemistry, Univ. Utah, Cent. Controlled Chemical Delivery, Biomedical Polymers Res. Building, Room 205, Salt Lake City, UT 84112, USA
SO Advanced Drug Delivery Reviews, (Feb. 1, 1999) Vol. 35, No. 2-3, pp. 289-306. print.
CODEN: ADDREP. ISSN: 0169-409X.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 13 Apr 1999
Last Updated on STN: 13 Apr 1999

L7 ANSWER 13 OF 23 MEDLINE on STN
AN 1998385856 MEDLINE
DN PubMed ID: 9720902

TI Synthesis of sulfonylurea **conjugated** copolymer via PEO spacer and its in vitro short-term bioactivity in **insulin** secretion from islets of Langerhans.
AU Hwang J S; Chae S Y; Lee M K; Bae Y H
CS Department of Materials Science and Engineering, Kwangju Institute of Science and Technology, South Korea.
SO Biomaterials, (1998 Jul) 19 (13) 1189-95.
Journal code: 8100316. ISSN: 0142-9612.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811
ED Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981124
AB In order to reduce the number of immunoprotected islets required in xeno- or allogenic transplants for reversing diabetes, analogues of glyburide (a sulfonylurea), an extremely hydrophobic **insulin** secretagogue, were synthesized and used in an attempt to produce water soluble sulfonylurea (SU) grafted polymers. After synthesizing various polymers containing glyburide analogues, a poly(N-vinyl-2-pyrrolidone-co-sulfonylurea succinyl PEO (Mw = 3000) acrylate) was found to be soluble in a cell culture medium at pH 7.4. However, solubility was only obtained by decreasing solution pH from 11 to 7.4. When the copolymer was added to the islet cell culture media at a concentration of 5 microg ml(-1) (based on the theoretical SU content of the copolymer), **insulin** secretion was enhanced by about 30% at low glucose concentrations of 50 and 100 mg dl(-1) compared to the control. This is equivalent to 40-60% bioactivity of glyburide. The polymer's effect on **insulin** secretion at a higher glucose concentration of 200 mg dl(-1) was not significant. Considering the previous results where a similar but insoluble polymer without a PEO spacer was used and the polymer showed SU bioactivity only at a glucose concentration of 50 mg dl(-1), the observations from this study indicates that the solubility of SU-grafted polymers may affect the binding of SU groups to SU receptors on the pancreatic beta-cells, resulting in improved pharmacodynamic effect of SU.

L7 ANSWER 14 OF 23 MEDLINE on STN DUPLICATE 4
AN 1998022057 MEDLINE
DN PubMed ID: 9376191
TI **Polyethylene glycol conjugated** **insulin**-like growth factor binding protein-1 (IGFBP-1) inhibits growth of breast cancer in athymic mice.
AU Van den Berg C L; Cox G N; Stroh C A; Hilsenbeck S G; Weng C N; McDermott M J; Pratt D; Osborne C K; Coronado-Heinsohn E B; Yee D
CS Department of Medicine, University of Texas Health Science Center, San Antonio 78284-7884, USA.
NC P30 CA 54174 (NCI)
P50 CA 58183 (NCI)
PO1 CA 30195 (NCI)
+
SO European journal of cancer (Oxford, England : 1990), (1997 Jun) 33 (7) 1108-13.
Journal code: 9005373. ISSN: 0959-8049.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711

ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971110

AB **Insulin**-like growth factor (IGF) binding protein-1 (BP-1) inhibits IGF-mediated proliferation of some breast cancer cell lines in vitro. Here we examined whether recombinant human wild-type IGFBP-1 (WT-BP-1) and IGFBP-1 **conjugated** with **polyethylene glycol** (PEG-BP-1) could inhibit breast cancer growth. Three breast cancer cell lines were used: MCF-7, MDA-MB-231 and MDA-MB-435A (ascites model). The cells were grown in agar with or without the BP-1 **conjugates** to investigate their effect on colony formation. Both WT-BP-1 and PEG-BP-1 inhibited anchorage-independent growth (AIG) of MCF-7 and MDA-MB-435A cells. AIG of MDA-MB-231 cells was not inhibited by PEG-BP-1, whereas WT-BP-1 significantly stimulated colony number. We also tested both forms of BP-1 in xenograft tumour models. Two solid breast tumour models were studied using MCF-7 and MDA-MB-231 cell lines, and one ascites model using the MDA-MB-435A cell line. PEG-BP-1 inhibited malignant ascites formation in the MDA-MB-435A model. Conversely, PEG-BP-1 did not significantly inhibit MCF-7 xenograft growth. However, the MDA-MB-231 tumour growth curves were significantly different by a constant amount, suggesting that PEG-BP-1 treatment inhibited early tumour growth of this cell line. In contrast, WT-BP-1 was ineffective in the MDA-MB-231 tumours. These data show that anti-IGF strategies can be used to inhibit breast cancer cell growth. Since PEG-BP-1 inhibited the in vivo, but not in vitro, growth of MDA-MB-231, we speculate that PEG-BP-1 may block host IGF functions required for optimal tumorigenesis. Because PEG-BP-1 has a prolonged serum half-life compared to WT-BP-1, we conclude that improvements in BP-1 pharmacological properties enhanced its antitumour effects in vivo.

L7 ANSWER 15 OF 23 MEDLINE on STN
AN 97467985 MEDLINE
DN PubMed ID: 9327129
TI Glucose-induced release of glycosylpoly(ethylene glycol) **insulin** bound to a soluble **conjugate** of concanavalin A.
AU Liu F; Song S C; Mix D; Baudys M; Kim S W
CS Department of Pharmaceutics and Pharmaceutical Chemistry/Center for Controlled Chemical Delivery, University of Utah, Salt Lake City 84112, USA.
NC DK 36598-10 (NIDDK)
SO Bioconjugate chemistry, (1997 Sep-Oct) 8 (5) 664-72.
Journal code: 9010319. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971128

AB Treatment of diabetes mellitus by **insulin** injections provides long-term control of the disease but lacks any feedback response to glucose concentration changes, which finally leads to a number of life-threatening conditions. The purpose of this study was to improve and optimize an implantable, concanavalin A (Con A) based, glucose-responsive **insulin** delivery system studied earlier [Jeong, S. Y., Kim, S. W., Holmberg, D. L., and McRea, J. C. (1985) J. Controlled Release 2, 143-152], which can be used for long-term diabetes treatment. To optimize the "**insulin** component" of the delivery system, we prepared PheB1 **insulin** amino group monosubstituted

monoglucosylpoly(ethylene glycol) (G-PEG) **insulin conjugates** (PEG M(r) 600 or 2000), which showed preserved bioactivity, significantly improved solubility and solution stability at neutral pH, and substantially suppressed hexamerization/dimerization. To improve the delivery system further, we synthesized and characterized a **conjugate** of Con A and monomethoxypoly(ethylene glycol) (mPEG, M(r) 5000) grafted hydrophilic poly(vinylpyrrolidone-co-acrylic acid) (PVPAA) with M(r) of 250,000. The optimal **conjugate** contained around eight PEG chains and two to three Con A tetramers attached through the amide bonds to the PVPAA chain. The Con A sugar binding characteristics were preserved, and, more importantly, Con A solubility at pH 7.4 substantially increased. This also holds true for a complex formed by the Con A **conjugate** and G-PEG **insulin**, which is soluble and does not precipitate under the physiologically relevant conditions under which the complex formed by the Con A **conjugate** and glycosyl **insulin** immediately precipitates. Finally, no leakage of the Con A **conjugate** from a membrane device was detected. Preliminary in vitro release experiments with Con A **conjugate** and G-PEG **insulin** complex enclosed in the membrane device showed a pulsative, reversible release pattern for G-PEG **insulin** in response to glucose challenges of 50-500 mg/dL, demonstrating the feasibility of the release system for use in planned, chronic in vivo studies with diabetic (pancreatectomized) dogs.

L7 ANSWER 16 OF 23 MEDLINE on STN
AN 97249463 MEDLINE
DN PubMed ID: 9095349
TI Mitogenic activities of water-soluble and -insoluble **insulin conjugates.**
AU Chen G; Ito Y; Imanishi Y
CS Department of Material Chemistry, Faculty of Engineering, Kyoto University, Japan.
SO Bioconjugate chemistry, (1997 Mar-Apr) 8 (2) 106-10.
Journal code: 9010319. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970724
Last Updated on STN: 19970724
Entered Medline: 19970717
AB **Insulin** was covalently bound to water-soluble polymers such as poly(oxyethylene) and poly(acrylic acid). The former and the latter product are water-soluble monovalent and multivalent **conjugates**, respectively. **Insulin** was also bound to a poly(acrylic acid)-grafted polystyrene film, to form a water-insoluble multivalent **conjugate.** The matrix polymer was prepared by graft polymerization of acrylic acid initiated by glow-discharged polystyrene film. **Insulin** coupled with poly(oxyethylene) reduced the mitogenic activity, but the poly(acrylic acid)-**insulin conjugate** stimulated cell growth more than native **insulin**. A concentration of immobilized **insulin** much lower than that of native **insulin** and the water-soluble **insulin conjugates** accelerated cell growth. The maximal mitogenic effect of the immobilized **insulin** was greater than that of native **insulin** or the water-soluble **insulin conjugates**. The findings suggest that the mitogenic effect of the water-insoluble, multivalent **insulin conjugate** lasts longer than that of the water-soluble **conjugates**, owing to the absence of

internalization into the cell.

L7 ANSWER 17 OF 23 MEDLINE on STN
AN 93105992 MEDLINE
DN PubMed ID: 1468454
TI **Insulin**-dependent diabetes mellitus and severe atopic dermatitis in a child with adenosine deaminase deficiency.
AU Notarangelo L D; Stoppoloni G; Toraldo R; Mazzolari E; Coletta A; Airo P; Bordignon C; Ugazio A G
CS Department of Paediatrics, Univérsity of Brescia, Italy.
SO European journal of pediatrics, (1992 Nov) 151 (11) 811-4.
Journal code: 7603873. ISSN: 0340-6199.
CY GERMANY: Germany, Federal Republic of
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199301
ED Entered STN: 19930212
Last Updated on STN: 19930212
Entered Medline: 19930127
AB We report a 2.3-year-old girl with complete lack of adenosine deaminase (ADA) activity who presented with severe atopic dermatitis and **insulin**-dependent diabetes mellitus but only mild recurrent infections. Abnormalities of immune function included profound depletion of CD8+ lymphocytes, hyperimmunoglobulinaemia E, and very low in vitro proliferative response to mitogens. Treatment with **polyethylene glycol-conjugated** ADA was followed by rapid amelioration of clinical and immunological conditions. The immunological and clinical features of this child suggest that the clinical spectrum of ADA deficiency may be broader than originally supposed.

L7 ANSWER 18 OF 23 MEDLINE on STN
AN 93004109 MEDLINE
DN PubMed ID: 1391478
TI Evaluation of a pyridoxylated hemoglobin polyoxyethylene **conjugate** solution as a perfusate for small intestine preservation.
AU Liu H; Agishi T; Kawai T; Hayashi T; Fujita S; Fuchinoue S; Takahashi K; Teraoka S; Ota K
CS Dept. of surgery III, Tokyo Women's Medical College, Japan.
SO Biomaterials, artificial cells, and immobilization biotechnology : official journal of the International Society for Artificial Cells and Immobilization Biotechnology, (1992) 20 (2-4) 557-61.
Journal code: 9111988. ISSN: 1055-7172.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199211
ED Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921118
AB A new type of artificial blood, pyridoxylated hemoglobin-polyoxyethylene **conjugate** (PHP) solution, (developed by PHP research group of the department of health and welfare of Japan, and produced by Ajinomoto Co., Inc. Tokyo) as an oxygen-carrying component, has been recently devised using hemoglobin obtained from hemolyzed human erythrocytes. Recently, the studies using this solution as a preservation solution were performed in some instances. To examine the mechanism of improved viability using this solution as a preservation solution, we developed a model of

orthotopic small intestine transplantation (OIT) in the rat. As a baseline study, we compared parameters of viability of the grafts preserved in Collins and UW solution to those preserved in PHP solution including a survival rate, a serum level total protein and albumin, and a change in body weight after transplantation. In our study, the simple hypothermia storage together with intestinal perfusion preservation with PHP solution was performed. Animals were divided into 6, 12, and 24 hr preservation groups. All of the rats survived after 6 hr preservation following transplantation. However, in 12 hr storage, five of six rats in PHP solution preservation survived and recovery in body weight after grafting was better than those with Collins and UW solution. We conclude that the PHP solution is, therefore, considered to possibly be a more suitable perfusate for small intestine preservation than Collins and UW solution.

L7 ANSWER 19 OF 23 MEDLINE on STN
AN 93004108 MEDLINE
DN PubMed ID: 1391477
TI Machine perfusion of isolated kidney at 37 degrees C using pyridoxalated hemoglobin-polyoxyethylene (PHP) solution, UW solution and its combination.
AU Horiuchi T; Ohta Y; Hashimoto K; Yamaguchi N; Dohi T; Uechi M; Watanabe T
CS Department of Precision Machinery Engineering, Faculty of Engineering, University of Tokyo, Japan.
SO Biomaterials, artificial cells, and immobilization biotechnology : official journal of the International Society for Artificial Cells and Immobilization Biotechnology, (1992) 20 (2-4) 549-55.
Journal code: 9111988. ISSN: 1055-7172.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199211
ED Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921118
AB To preserve isolated kidney normothermically, PHP containing UW components were evaluated as perfusates. Kidneys were flushed out by Lactate Ringer solution immediately after isolation from mongrel dogs, and then connected to the perfusion circuit which consists of a preservation box, a reservoir of perfusate, a membrane oxygenator and a drive unit. PHP containing 140 mEq/l of Na+ and 4 mEq/l of K+ (PHP(E)), UW solution (UW) and UW components added PHP(E) were prepared and adjusted at pH 7.4 prior to use. Temperature and perfusion pressure were controlled at 37 degrees C and 100 mmHg, respectively. During 12 hour perfusion, remarkable changes in pH were seen in UW group and PHP group while higher oxygen consumption was noted in PHP(E)+UW group than that in PHP(E) group. The histological findings showed moderate damages of tubular epithelial cells and maintaining normal glomerular structure in PHP(E)+UW while severe damage of both tubulus in UW group were seen. There was no edematous degeneration in both UW and PHP(E)+UW groups, however, it was seen in PHP(E) alone. It was suggested that components of UW solution have positive effect on normothermic machine perfusion with PHP(E) solution.

L7 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1988:200066 BIOSIS
DN PREV198885101412; BA85:101412
TI A HIGHLY SENSITIVE ENZYME IMMUNOASSAY OF ANTI-**INSULIN** ANTIBODIES IN HUMAN SERUM.
AU KOHNO T [Reprint author]; ISHIKAWA E; SUGIYAMA S; NAKAMURA S; KANEMARU Y

CS DEP BIOCHEM, MED COLL MIYAZAKI, KIYOTAKE, MIYAZAKI 889-16, JPN
SO Journal of Clinical Laboratory Analysis, (1987) Vol. 1, No. 2, pp. 170-174.
CODEN: JCANEM. ISSN: 0887-8013.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 21 Apr 1988
Last Updated on STN: 21 Apr 1988
AB A highly sensitive enzyme immunoassay of anti-**insulin** antibodies in human serum is described. Serum samples were subjected to successive processes of the incubation with **insulin**, the dextran-charcoal treatment to remove free **insulin**, the precipitation of **insulin** anti-**insulin** antibodies by **polyethylene glycol**, the acid treatment of the precipitates to inactivate anti-**insulin** antibodies, and the measurement of **insulin** by sandwich enzyme immunoassay technique. By this enzyme immunoassay, anti-**insulin** antibodies were demonstrated in most of serum samples from patients who had been treated with **insulin** for 0.6-24 months. The detection limit of anti-**insulin** IgG in human serum was 1,000 to 3,000-fold less than that obtained by the previously reported enzyme immunoassay, in which an **insulin**-coated polystyrene ball was incubated with diluted serum and subsequently with (antihuman IgG γ-chain) Fab'-horseradish peroxidase **conjugate.** The present enzyme immunoassay may be useful for the measurement of antibodies for not only **insulin** but also other antigens that are not precipitated by **polyethylene glycol.**

L7 ANSWER 21 OF 23 MEDLINE on STN DUPLICATE 5
AN 88027818 MEDLINE
DN PubMed ID: 2444366
TI A highly sensitive enzyme immunoassay of anti-**insulin** antibodies in human serum.
AU Kohno T; Ishikawa E; Sugiyama S; Kamano M; Kuzuya H; Imura H
CS Department of Biochemistry, Medical College of Miyazaki, Japan.
SO Clinica chimica acta; international journal of clinical chemistry, (1987 Sep 15) 168 (1) 97-107.
Journal code: 1302422. ISSN: 0009-8981.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198712
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871201
AB A highly sensitive enzyme immunoassay of anti-**insulin** antibodies in human serum is described. Serum samples were subjected to successive processes of incubation with **insulin**, dextran-charcoal treatment to remove free **insulin**, precipitation of **insulin**-anti-**insulin** antibodies by **polyethylene glycol**, acid-treatment of the precipitates to inactivate anti-**insulin** antibodies and measurement of **insulin** by sandwich enzyme immunoassay technique. The detection limit of anti-**insulin** IgG in human serum was 50 pg/assay or 450 ng/l of serum. This was 1,000- to 3,000-fold less than that obtained by a conventional enzyme immunoassay, in which an **insulin**-coated polystyrene ball was incubated with diluted serum and subsequently with (anti-human IgG gamma-chain) Fab'-horseradish peroxidase **conjugate.** By the present enzyme immunoassay, anti-**insulin** antibodies were demonstrated in most

(89%) of serum samples from diabetic patients who had been treated with porcine **insulin** and porcine **insulin** plus bovine **insulin** for 0.6-10 mth, while only a small proportion (3%) of serum samples from the same patients was positive by the conventional enzyme immunoassay. Similar results were obtained with serum samples from diabetic patients who had been treated with human **insulin** for 0.5-8.2 mth. The present enzyme immunoassay may be useful for the measurement of antibodies not only for **insulin** but also other antigens which can be removed by dextran-charcoal treatment and are not precipitated by **polyethylene glycol.**

L7 ANSWER 22 OF 23 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1986:416116 BIOSIS
DN PREV198682091650; BA82:91650
TI A HIGHLY SENSITIVE ENZYME IMMUNOASSAY OF ANTI-**INSULIN** ANTIBODIES IN GUINEA-PIG SERUM.
AU KOHNO T [Reprint author]; RUAN K-H; ISHIKAWA E
CS DEP OF BIOCHEMISTRY, MED COLL OF MIYAZAKI, KIYOTAKE, MIYAZAKI 889-16, JAPAN
SO Analytical Letters, (1986) Vol. 19, No. 9-10, pp. 1083-1096.
CODEN: ANALBP. ISSN: 0003-2719.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 25 Oct 1986
Last Updated on STN: 25 Oct 1986
AB A highly sensitive enzyme immunoassay of anti-**insulin** antibodies in guinea pig serum is described. Guinea pig anti-**insulin** serum was diluted to various extents with nonspecific guinea pig serum and incubated with **insulin.** **Insulin** bound to anti-**insulin** antibodies was separated from free **insulin** by precipitation with **polyethylene glycol.** Anti-**insulin** antibodies in the precipitates were dissociated from **insulin** and inactivated by incubation with 0.1 mol/l HCl. The amount of **insulin** dissociated was measured by sandwich enzyme immunoassay using anti-**insulin** IgG-coated polystyrene balls and affinity-purified anti-**insulin** Fab'-horseradish peroxidase **conjugate.** The detection limit of anti-**insulin** antibodies in guinea pig serum was improved 1,000-fold as compared with that of the enzyme immunoassay previously described, in which **insulin**-coated polystyrene balls were incubated with diluted guinea pig anti-**insulin** serum and subsequently with rabbit (anti-guinea pig IgG) Fab'-horseradish peroxidase **conjugate.**

L7 ANSWER 23 OF 23 MEDLINE on STN
AN 79211700 MEDLINE
DN PubMed ID: 222503
TI Human corticotropin (ACTH) radioimmunoassay with synthetic 1--24 ACTH.
AU Kao P C; Jiang N S; Carpenter P C
SO Clinical chemistry, (1979 Jul) 25 (7) 1267-73.
Journal code: 9421549. ISSN: 0009-9147.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197909
ED Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19790917
AB A corticotropin antiserum was obtained from rabbits immunized with

synthetic 1--24 corticotropin **conjugated** with bovine serum albumin. The antiserum did not cross react with synthetic alpha-melanotropin or with synthetic beta-endorphin and had a cross reactivity of 0.23% with human beta-lipotropin. We developed a radioimmunoassay with the antiserum obtained, in which we used **polyethylene glycol** in conjunction with a second precipitating antibody for fast (15-min) separation of antibody-bound and free corticotropin. The assay had a sensitivity of 16 ng/L and was validated on patients with various pituitary and adrenal diseases. From 103 normal subjects, the median value for corticotropin in specimens collected during the morning was 34 ng/L of plasma; the upper 95% confidence limit of the normal range was 98 ng/L.

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L8 17 SEA FILE=WPIDS ABB=ON PLU=ON INSULIN(L) OLIGOMER? (L) CONJUGAT?
L9 48712 SEA FILE=WPIDS ABB=ON PLU=ON POLYETHYLENE GLYCOL OR ALKYLENE GLYCOL OR PEG OR POLY (2W) (ETHYLENE OR ALKYLENE) (W) GLYCOL
L10 8 SEA FILE=WPIDS ABB=ON PLU=ON L8 AND L9

=> d .wp 1-8

L10 ANSWER 1 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-487834 [46] WPIDS
DNC C2004-181748
TI Composition used to increase oral absorption rate of polar active substance, comprises polar active substance, organic alkalizing agent and surfactant.
DC B05 B07
IN CHOI, M; HONG, C; KI, M; SHIN, H
PA (CHON-N) CHONG KUN DANG PHARM CORP; (MCTE-N) MC TECHNOLOGIES INC
CYC 106
PI WO 2004052405 A1 20040624 (200446)* EN 30
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT WO 2004052405 A1 WO 2003-KR2700 20031210
PRAI KR 2002-78778 20021211
AB WO2004052405 A UPAB: 20040720
NOVELTY - Composition used for oral absorption of a polar active substance (I) comprises at least one polar active substance (A), at least one organic alkalizing agent having an amino acid or polyol structure (B) and at least one surfactant having a 6-18C fatty acid structure (C).

DETAILED DESCRIPTION - Composition for oral absorption of a polar active substance (I) comprises at least one polar active substance (A) having a bioavailability of less than 30% which is poorly absorptive through lipid membranes because of its high hydrophilicity and charged ion, at least one organic alkalizing agent having an amino acid or polyol structure (B) which shows alkalinity in aqueous solution and is ionically bonded to the polar active substance and at least one surfactant having a 6-18C fatty acid structure (C) which has a hydrophilic-lipophilic balance (HLB) value of 4-18.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition for oral absorption of a polar active substance, which comprises (A) and at least one organic alkalizing agent having a fatty acid ester structure (D), which shows alkalinity in aqueous solution and is ionically bonded to the polar active substance.

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - The composition is useful to increase the oral absorption rate of the polar active substance.

ADVANTAGE - (I) increases the oral absorption rate of the polar active substance and its bioavailability. (I) was tested for its bioavailability in rats. The results showed that (I) exhibited a high bioavailability of 20-110% and (I) increased the oral absorption of the active substances having an oral absorption rate as low as 3% by 5-25 times.

Dwg.0/7

TECH UPTX: 20040720
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (A) Comprises cephaloridine, ceftiofur, cefixime, cefepime, cefoperazone, cefotaxime, ceftazidime, ceftriaxone, moxalactam, gentamicin, aztreonam, amikacin, isepamycin, netilmicin, tobramycin, vancomycin, daptomycin, teicoplanin, polymixin-B, bacitracin, heparin, parathyroid hormone, growth hormone and/or **insulin**. The organic alkalizing agent having an amino acid structure comprises aminoacids, amino acid derivatives and/or peptides and the organic alkalizing agent having a polyol structure

comprises alkaline saccharides, their **oligomers** and/or polymers prepared from upto 20 alkaline saccharides as monomers, and saccharide-like compounds.
(C) Comprises sugar fatty acid esters, saccharin fatty acid esters, glycerol fatty acid esters, propylene glycol fatty acid esters, **polyethylene glycol** fatty acid esters, sorbitan fatty acid esters and/or polysorbitan fatty acid esters. (D) Comprises alkaline substance prepared from the dehydration between the hydroxy group of a fatty acid ester and a carboxy group of an amphoteric compound having both an amine group and a carboxy group.
The active substance and the organic alkalizing agent are present in a charge ratio of 10:1-1:10. (A) has at least one anionic group and has a partition coefficient (Log P) of upto 1.5. The polar active substance and the organic alkalizing agent are combined with each other to form a hydrophobic **conjugate** having a size of 10 nm-100 micro-m in the aqueous phase.
Preferred Composition: The active substance forms a hydrophobic **conjugate** with intestinal juices after orally administering in the solid state.
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The composition also comprises at least one excipient such as disintegrating agents, suspending agents, thickening agents, lubricating agents, sweetening agents, plasticizers or preservatives. The composition is formulated into syrups, dry syrups, powdery granules, tablets or capsules and the composition is enteric coated when the active substance is unstable to gastric acid.

L10 ANSWER 2 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-224429 [21] WPIDS
DNC C2004-088587
TI Novel polyalkyleneamine-containing oligomeric compound useful for preventing or delaying infection, inflammation or tumor formation in organisms.
DC A26 A96 B04 D16
IN GUZAEV, A P; MAIER, M A; MANOHARAN, M
PA (GUZA-I) GUZAEV A P; (MAIE-I) MAIER M A; (MANO-I) MANOHARAN M
CYC 1
PI US 2004019000 A1 20040129 (200421)* 37
ADT US 2004019000 A1 US 2002-199585 20020719
PRAI US 2002-199585 20020719
AB US2004019000 A UPAB: 20040326
NOVELTY - A polyalkyleneamine-containing oligomeric compound (OC), is new.
DETAILED DESCRIPTION - A polyalkyleneamine-containing oligomeric compound (OC) comprising formula I or VI, is new.
T1 = hydroxyl or a protected hydroxyl;
Bx = optically protected heterocyclic base part;
R1 = hydrogen or a sugar substituent group;
X = S or O;
n = 2-50;
R2 and R3 = -L-R4, hydrogen or a sugar substituent group;
L = linking group;
s = 0 or 1; and
R4, R4a and R4b = polyethylenamino radical.
Where polyethylenamino radical has a molecular weight of 100-100000 Dalton. If R4a or R4b is not a polyethylenamino radical, it is hydrogen, an amino protecting group, a carbonyl protecting group, -C(O)R5, substituted or unsubstituted 1-10C alkyl, substituted or unsubstituted 2-10C alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group, a reporter group, a conjugate group, a D or L alpha -amino acid linked through the alpha -carboxyl group or optionally through omega -carboxyl

group, when the amino acid is aspartic acid or glutamic acid, or a peptide derived from D, L or mixed D and L amino acids linked through a carboxyl group, where the substituent groups are chosen from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thio, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl.

INDEPENDENT CLAIMS are also included for:

(1) a compound (C) comprising an oligomeric part, a fusogenic part, and a targeting part; and

(2) enhancing (M1) the cellular uptake of OC, by conjugating OC to a fusogenic part.

ACTIVITY - Antimicrobial; Antiinflammatory; Cytostatic.

No biological data given.

MECHANISM OF ACTION - Inhibitor of gene expression. No biological data given.

USE - OC is useful as prodrug, useful in diagnostics, therapeutics and as research reagents and kits. OC is useful for preventing or delaying infection, inflammation or tumor formation in organisms.

Dwg.0/2

TECH UPTX: 20040326

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred **Oligomeric** Compound: In OC, R3 is preferably -L-R4. In OC, R4 is a polyethylenamino radical of formula II.

q = 2-1700; and

R5 = H or formula III.

p = 1-1000; and

R6 = H or formula II.

Preferably R5 is H or formula III. L is a linking group of formula IV or V.

R8 = -O-, phosphate or phosphorothioate;

R9 = (CH2)m, (CH2)mm-6-20C aryl or a **polyethylene glycol** -(CH2)2-(O-(CH2)2)mmm-; and

m, mm or mmm = 1-6.

Where R8 is covalently attached to R2 or R3 position of formula I.

Preferred Compound: In (C), the fusogenic part is covalently linked to the **oligomeric** part. The targeting part is covalently linked to the **oligomeric** or fusogenic part, where the fusogenic part is a lipophilic polyamine, polyethylenimine, polyalylamine, fusogenic peptide, **oligomeric** imidazole, histidine, pyridine, hydroxylamine, substituted hydroxylamine, hydrazine, substituted hydrazine, thiourea or imine. The targeting part is a ligand that binds to a cellular reporter, where the targeting part is transferring, folate, epidermal growth factor, nerve growth factor, **insulin**, alpha-fetoprotein, galactose, galactosamine, lactose, mannose, a polyclonal antibody, monoclonal antibody, vitamin B12, ibuprofen, cholesterol, low-density lipoprotein, peptide comprising an arginine-glycine-aspartic acid sequence. The **oligomeric** part is an oligonucleotide, and oligonucleotide analog, a peptide nucleic acid or a peptide nucleic acid analog.

Preferred Method: (M1) further involves **conjugating** **oligomeric** compound-fusogenic part **conjugate** to a targeting part. The targeting part is covalently linked to **oligomeric** compound or fusogenic part. The targeting part is a ligand that binds to a cellular receptor.

L10 ANSWER 3 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-051257 [05] WPIDS
CR 2004-010111 [01]
DNC C2004-020644
TI Increasing serum half-life of biologically active agent involves fusing biologically active agent to transthyretin or a transthyretin variant.
DC A96 B04 D16

IN WALKER, K; XIONG, F
PA (WALK-I) WALKER K; (XION-I) XIONG F
CYC 1
PI US 2003195154 A1 20031016 (200405)* 61
ADT US 2003195154 A1 CIP of US 2002-117109 20020404, US 2003-407078 20030403
PRAI US 2003-407078 20030403; US 2002-117109 20020404
AB US2003195154 A UPAB: 20040120
NOVELTY - Increasing (M1) the serum half-life of a biologically active agent involves fusing the biologically active agent to transthyretin (TTR) or a TTR variant.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a substantially homogenous preparation (I) of a TTR-biologically active agent fusion or TTR variant-biologically active agent fusion, optionally in diluent, carrier or adjuvant;

(2) a substantially homogenous preparation (II) of a **polyethylene glycol** (**PEG**)-TTR-biologically active agent fusion or **PEG**-TTR variant-biologically active agent fusion, optionally in a diluent, carrier or adjuvant;

(3) preparing a substantially homogenous preparation of a TTR-biologically active agent fusion involves fusing the TTR to a biologically active agent to provide a TTR-biologically active agent fusion and isolating the TTR-biologically active agent fusion;

(4) preparing a substantially homogenous preparation of a TTR variant-biologically active agent fusion involves engineering a cysteine residue into a specific amino acid position within the amino acid sequence of the TTR to provide a variant of the TTR; fusing the TTR variant to a biologically active agent to provide a TTR variant-biologically active fusion and isolating the TTR variant-biologically active agent fusion;

(5) preparing a substantially homogenous preparation of a **PEG**-TTR-biologically active agent fusion involves **conjugating** a **polyethylene glycol** to the TTR to provide a **PEG**-TTR fusing the **PEG**-TTR to a biologically active agent to provide a **PEG**-TTR-biologically active agent fusion and isolating the **PEG**-TTR- biologically active agent fusion;

(6) preparing a substantially homogenous preparation of a **PEG**-TTR variant-biologically active agent fusion comprising engineering a cysteine residue into a specific amino acid position within the amino acid sequence of the TTR to provide a variant of the TTR, **conjugating** a **polyethylene glycol** to the TTR variant at the cysteine residue to provide a **PEG**-TTR variant fusing the **PEG**-TTR variant to a biologically active agent to provide a **PEG**-TTR-biologically active agent fusion, and isolating the **PEG**-TTR biologically active agent fusion;

(7) a fusion protein (III) comprising a TTR protein fused to a heterologous sequence; and

(8) a nucleic acid encoding (III)..

ACTIVITY - Hemostatic; Antidiabetic; Antianemic; Dermatological; Immunosuppressive; Antiinflammatory; Cytostatic.

MECHANISM OF ACTION - Increases half life of TMP and GLP-1 in vivo. Effect of injecting TPO-mimetic peptide (TMP) (m-) transthyretin (TTR) into mice on blood platelet count was tested as follows. 50 BDF1 mice were split into 5 groups and injected subcutaneously with either diluting agent or diluting agent with 50 micro g test protein per kg animal. Each group was divided into half and bled (140 micro l) on alternate time points (day 0, 3, 5, 7, 11, 12, 14 and 17). Mice were anesthetized with isoflurance prior to collection. The collected blood was analyzed for complete and differential count. Fc-TMP showed the greatest response with platelet count peaking at 4.3 multiply 1012 platelets L-1 on day 5, which is over 3.4 times baseline at 1.2 multiply 1012 platelets L-1. TMP(m)-TTR-

polyethylene glycol (**PEG**) 5K was a moderate responder peaking at 2.3 multiply 1012 platelets L-1 which is just under twice the baseline level. The non-pegylated form of TMP(m)-TTR showed very little response at 1.5 multiply 1012 platelets L-1 which is only 20% over the baseline level. The non-pegylated form of TMP (m)-TTR showed better binding in vitro than its pegylated counterparts, but it has poor performance in vivo compared to TMP (-m)-TTR-**PEG** 5k. This indicates that **PEG** is required to improve the biological half-life of the TTR construct, and this more than compensates for the reduced affinity for the receptor. The results showed that the half-life of biologically active agent was increased.

USE - (M1) is useful for increasing the serum half-life of a biologically active agent. (I) and (II) comprising TMP is useful for treating thrombocytopenia. (I) and (II) comprising GLP-1 is useful for treating non-**insulin** dependent diabetes (claimed). (I) and (II) comprising TMP is useful for treating megakaryocyte/platelet deficiency/thrombocytopenia. Specific diseases that involves thrombocytopenia e.g., aplastic anemia, idiopathic thrombocytopenia, metastatic tumors which result in thrombocytopenia, systemic lupus erythematosus, splenomegaly, Fanconi's syndrome, vitamin B12 deficiency, folic acid deficiency, May-Hegglin anomaly, Wiskott-Aldrich syndrome, and paroxysmal nocturnal hemoglobinuria can be treated. TMP compounds are useful in stimulating certain cell types other than megakaryocyte, which expresses Mpl receptor and in maintaining the viability or storage life of platelets and related cells.

DESCRIPTION OF DRAWING(S) - The figure shows the size exclusion chromatography of fusion of peptides to the amino terminus or carboxy terminus of a TTR variant, TTR (C10A/G83C), does not alter its **oligomeric** structure.

Dwg.2/15

TECH UPTX: 20040120

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M1) TTR or TTR variant is chemically modified with the chemical chosen from dextran, poly(n-vinyl pyurrolidone), propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols polyvinyl alcohols and preferably **polyethylene glycol.**

PEG has a molecular weight of 1-100 kD, preferably 5-30 kD. TTR is encoded by nucleic acid having a fully defined sequence of 387 base pairs (bp) as given in the specification and the TTR-variant is encoded by a nucleic acid having a fully defined sequence of 387 bp as given in the specification. The biologically active agent is a protein or a peptide. The peptide is a TPO-mimetic peptide (TMP). The biologically active agent is a glucagon-like peptide-1 (GLP-1).

Preferred Preparation: In (I) and (II) the biologically active agent is a protein or a peptide. The peptide is TMP or GLP-1. In (II) the fusion contains a linker peptide.

Preferred Fusion Protein: In (III) the heterologous sequence is a TMP or GLP-1. (III) comprises a linker sequence between the TTR protein and the heterologous sequence.

L10 ANSWER 4 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-221302 [21] WPIDS
DNC C2003-056080
TI Monodispersed mixture of conjugates useful in treatment of disease e.g. diabetes comprises drug coupled to oligomer containing polyalkylene glycol moiety.
DC A96 B04 D16
IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L; PRICE, C H
PA (NOBE-N) NOBEX CORP; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H

CYC 101
PI WO 2002098446 A1 20021212 (200321)* EN 101
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
BR 2001006401 A 20030211 (200321)
JP 2003104913 A 20030409 (200333) 308
US 2003228275 A1 20031211 (200382)
EP 1404355 A1 20040407 (200425) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002098446 A1 WO 2002-US17567 20020604; BR 2001006401 A BR 2001-6401 20011011; JP 2003104913 A JP 2001-317307 20011015; US 2003228275 A1 US 2001-873797 20010604; EP 1404355 A1 EP 2002-737357 20020604, WO 2002-US17567 20020604
FDT EP 1404355 A1 Based on WO 2002098446
PRAI US 2001-873797 20010604
AB WO 200298446 A UPAB: 20030328

NOVELTY - A substantially monodispersed mixture of **conjugates** comprises a drug coupled to an **oligomer** (a) containing a polyalkylene glycol moiety (b).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for synthesizing a monodispersed mixture of **conjugate**, that involves:

(i) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a substantially monodispersed mixture containing compounds of formula R2(OC2H4)q-OMs (II) to form a monodispersed mixture comprising polymers of formula R2(OC2H4)m+q-OR1 (III);

(ii) activating (III) to form a monodispersed mixture of activated polymers capable of reacting with a drug; and

(iii) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to form a monodispersed mixture of **conjugates** comprising drug coupled to an **oligomer** containing **polyethylene glycol** with m+p subunits.

R1 and R2 = H or lipophilic moiety;
m, q = 1 - 25; and
X+ = positive ion.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - In the treatment of disease states e.g. **insulin** deficiency.

Male CF-1 mice were housed in a room. Mice were acclimated to housing conditions for 48 - 72 hours prior to the day of experiment. Prior to dosing, mice were fasted overnight and water was provided ad libitum. Mice were distributed into groups of five animals per time point and were administered a single oral dose of a PEG7-octyl-(sCT), diconjugate (Octyl Di) (test) or salmon calcitonin (sCT or Calcitonin) for comparison purposes. Oral doses were administered at 10 ml/kg in a phosphate-buffered PEG7-octyl-sCT, diconjugate formulation. The buffered formulation was prepared by adding phosphate buffer (80 mL) in a beaker. The sodium cholate was added to the phosphate buffer with stirring until dissolved. The deoxy cholate was then added and stirring was continued until dissolved. The PEG7-octyl-sCT, diconjugate, solution was added. The remaining phosphate buffer was added to achieve a final weight of 100 g. Dose-response curves were constructed. At appropriate time points, mice were ether-anesthetized, the vena cavae exteriorized, and blood samples

were obtained. Blood aliquots were clotted at 22 deg. C for 1 hour, and the sera removed and pipetted into a clean receptacle. Total serum calcium was determined for each animal. Serum calcium data were plotted and pharmacokinetic parameters determined. Means and standard deviations (or standard errors) were calculated and plotted to determine effect differences among dosing groups. The % baseline calcium drop at 2 micro g/kg dose for the test was 21%. The in vitro activity of PEG7-octyl-sCT and PEG7-decyl-sCT mono- and diconjugates, the stearate-PEG6-sCT, diconjugate, and stearate-PEG8-sCT, diconjugate, appeared to have in vivo activity that was comparable with the in vivo activity observed for the PEG7-octyl-sCT and PEG7-decyl-sCT, mono- and di-**conjugates.** The improved in vivo activity of the stearate containing **conjugates** indicated that these **conjugates** were undergoing hydrolysis in vivo to provide an active salmon calcitonin or active salmon calcitonin-**PEG conjugate.**

ADVANTAGE - The mixture exhibits greater in vivo/in vitro activity than the in vivo/in vitro activity of the polydispersed mixture of drug-**oligomer conjugates** having same number of average molecular weight as the mixture. The mixture has increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of **insulin** drug-**oligomer conjugate** mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of **insulin** drug-**oligomer conjugates** having same number average molecular weight as the mixture.

Dwg.0/43

TECH UPTX: 20030328

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred **Conjugates**: The mixture has a dispersity coefficient (DC) greater than 10000 (preferably greater than 100000, especially greater than 500000) daltons as given in formula (X) or has molecular weight distribution with a standard deviation of less than 22 (preferably less than 14, especially less than 11) daltons. In each **conjugate**, the **oligomer** has the optionally same number of polyalkylene glycol subunit. When each **conjugate** has same molecular weight, the **conjugate** has formula Drug-(B'-Lh-Gi-Ra-G'j-R'b-Qk-T)p-. The **conjugate** is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes. At least 96, 97, 98 or 99% of the **conjugate** in the mixture has the same molecular weight. Each **conjugate** comprises several **oligomers.**

n = number of different molecules in the sample;
Ni = number of ith molecules in the sample;
Mi = mass of the ith molecule;
B' = bonding moiety;
L = linking moiety;
G, G' and Q = spacer moiety;
R' = lipophilic moiety or polyalkylene glycol (preferably **polyethylene glycol** having 7 **polyethylene glycol** subunits);
R = lipophilic moiety or polyalkylene glycol;
T = terminating moiety;
i, j, k = 0 or 1 (preferably 0);
a and b = 0 or 1 (preferably 1);
h = 0 or 1;
p = 1 - number of nucleophilic residues on the drug; and
provided that:
(a) when R is the polyalkylene glycol moiety then a is 1; and
(b) when R' is the polyalkylene glycol moiety then b is 1.
Preferred Method: The method further involves:

(i) reacting a monodispersed mixture comprising compounds of formula R2(OC2H4)q-OH (V) with a methanesulfonyl chloride to form a monodispersed mixture comprising (II);
(ii) reacting a monodispersed mixture comprising compounds of formula R2-OMs (VI) with a monodispersed mixture comprising compounds of formula R3(OC2H4)m-O- X+2 (VII) to form a monodispersed mixture comprising compounds of formula R3(OC2H4)m-OR2 (VIII);
(iii) reacting (VIII) to form a mixture comprising (V);
(iv) reacting a monodispersed mixture comprising a compound of formula R1(OC2H4)q-OH (IV) to form the substantially monodispersed mixture comprising (I).
R3 = benzyl, trityl or THP;
X+2 = positive ion.
The activating of the mixture involves reaction of (III) with N-hydroxy succinimide to form an activated polymer capable of reacting with a drug. The reaction of mixture of activated polymers with a monodispersed mixture of polypeptides involves reacting the mixture with at least one functionality of the polypeptide to form monodispersed mixture of **conjugates** comprising the polypeptide coupled to an **oligomer** containing **polyethylene glycol** with m+q subunits.

TECHNOLOGY FOCUS - POLYMERS - Preferred **Oligomer**: (a) is devoid of lipophilic moiety. (a) is covalently coupled to the drug or a nucleophilic residue of the polypeptides. (a) further comprises a lipophilic moiety optionally covalently coupled to the second **polyethylene glycol.** Each **oligomer** of the several **oligomers** is same. (a) comprise a first polyalkylene glycol moiety covalently coupled to the drug by a non-hydrolyzable bond and a second polyalkylene glycol covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond. The drug in synthesis method is a polypeptide.
Preferred Components: (b) has at least 2, 3 or 4 (preferably at least 5 or 6, especially at least 7) polyalkylene glycol subunits. (b) is lower alkyl polyalkylene glycol (preferably **polyethylene glycol** or uniform polypropylene glycol).
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Drug: The drug is a polypeptide. The polypeptide is adrenocorticotropic hormone peptide, adrenomedullin peptide, allatostatin peptide, amylin peptide, amyloid beta-protein fragment peptide, angiotensin peptide, antibiotic peptide, antigenic polypeptide, anti-microbial peptide, apoptosis related peptide, atrial natriuretic peptide, bag cell peptide, bombesin peptide, bone GLA peptide, bradykinin peptide, brain natriuretic peptide, C-peptide, C-type natriuretic peptide, calcitonin peptide, calcitonin gene related peptide, CART peptide, casomorphin peptide, chemotactic peptide, cholecystokinin peptide, colony-stimulating factor peptide, corticortropin releasing factor peptide, cortistatin peptide, cytokine peptide, dermorphin peptides, dynorphin peptide, endorphin peptide, endothelin peptide, ETa receptor antagonist peptide, ETb receptor antagonist peptide, enkephalin peptide, fibronectin peptide, galanin peptide, gastrin peptide, glucagon peptide, Gn-RH associated peptide, growth factor peptide, growth hormone peptide, GTP-binding protein fragment peptide, guanylin peptide, inhibin peptide, **insulin** peptide, interleukin peptide, laminin peptide, leptin peptide, leucokinin peptide, luteinizing hormone-releasing hormone peptide, mastoparan peptide, mast cell degranulating peptide, melanocyte stimulating hormone peptide, morphiceptin peptide, motilin peptides neuro-peptide, neuropeptide Y peptide, neurotropic factor peptide, orexin peptide, opioid peptide, oxytocin peptide, PACAP peptide, pancreastatin peptide, pancreatic polypeptide, parathyroid hormone peptide, parathyroid hormone-related peptide, peptide T peptide, prolactin-releasing peptide,

peptide YY peptide, renin substrate peptide, secretin peptide, somatostatin peptide, substance P peptide, tachykinin peptide, thyrotropin-releasing hormone peptide, toxin peptide, vasoactive intestinal peptide, vasopressin peptide, or virus related peptide.

L10 ANSWER 5 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-210058 [20] WPIDS
DNC C2003-053443
TI Monodispersed mixture of **conjugates** useful in the treatment of diabetes comprises an **insulin** drug coupled to an **oligomer** containing a **polyethylene glycol** moiety.
DC A25 A96 B04
IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L; PRICE, C H; RADHAKRISHNAN, B
PA (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2002098232 A1 20021212 (200320)* EN 64
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003027748 A1 20030206 (200320)
BR 2001006851 A 20030408 (200329)
JP 2003113113 A 20030418 (200335) 182
EP 1404178 A1 20040407 (200425) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2004004692 A 20040113 (200434)
ADT WO 2002098232 A1 WO 2002-US17574 20020604; US 2003027748 A1 US 2001-873899 20010604; BR 2001006851 A BR 2001-6851 20011011; JP 2003113113 A JP 2001-316998 20011015; EP 1404178 A1 EP 2002-737359 20020604, WO 2002-US17574 20020604; KR 2004004692 A KR 2003-715910 20031204
FDT EP 1404178 A1 Based on WO 2002098232
PRAI US 2001-873899 20010604
AB WO 200298232 A UPAB: 20030324
NOVELTY - A substantially monodispersed mixture of **conjugates** comprising an **insulin** drug coupled to an **oligomer** (a) containing a **polyethylene glycol** moiety (b), is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a substantially monodispersed mixture of **conjugates** (A') comprising human **insulin** covalently coupled at Lys-B29 of the human **insulin** to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated **polyethylene glycol** having at least 7 **polyethylene glycol** subunits; and
(2) a method of synthesizing a monodispersed mixture of **conjugates** comprising:
(i) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a substantially monodispersed mixture comprising compound of formula R2(OC2H4)n1-OMs (II) to provide a monodispersed mixture comprising polymers of formula R2(OC2H4)m+n1-OR1 (III);
(ii) activating (III) to provide a monodispersed mixture of activated polymers capable of reacting with **insulin** drug; and
(iii) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to provide a monodispersed mixture of **conjugates** comprising **insulin** drug coupled to an

oligomer containing **polyethylene glycol** with m+n1 subunits.
R, R2 = H or lipophilic moiety;
m, n1 = 1-25;
X+ = positive ion.
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - None given.
USE - The mixture is used in the treatment of **insulin** deficiency in a subject (claimed).
ADVANTAGE - The mixture exhibits greater in vivo/vitro activity than the in vivo/vitro activity of the polydispersed mixture of **insulin** drug-**oligomer conjugates** having same number of average molecular weight as the mixture respectively. The mixture has increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of **insulin** drug-**oligomer conjugate** mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of **insulin** drug-**oligomer conjugates** having same number average molecular weight as the mixture.
Dwg.0/21

TECH UPTX: 20030324
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred **Conjugates**: The mixture has dispersity coefficient (DC) greater than 10000 (preferably greater than 100000, especially less than 500000) as given by a formula (i) or has molecular weight distribution with a standard deviation of less than 22 (preferably less than 14, especially less than 11) Daltons.
The mixture has optionally same number of **polyethylene glycol** subunits. When each **conjugate** is same in the mixture, the each **conjugate** has formula **Insulin** Drug-(B'-Lh-Gi-Rm'-G'j-R'n'-Qk-T)p-.
The **conjugate** is amphiphilically balanced such that the **conjugate** is aqueously soluble and able to penetrate biological membranes. At least 96, 97, 98 or 99% of the **conjugates** in the mixture has same molecular weight. In (A'), each **conjugate** comprises human **insulin** covalently coupled at Lys-B29 of the human **insulin** to the carboxylic acid moiety of hexanoic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated **polyethylene glycol** moiety having 7 **polyethylene glycol** subunits.
n = number of different molecules in the sample;
Ni = number of ith molecules in the sample;
Mi = mass of the ith molecule;
B' = bonding moiety (preferably carbonyl);
L = linking moiety;
G, G', Q = spacer moiety;
R' = lipophilic moiety or polyalkylene glycol (preferably **polyethylene glycol** having 7 **polyethylene glycol** subunits);
R = lipophilic moiety or polyalkylene glycol (preferably 5C alkylene);
T = terminating moiety (preferably methoxy);
k, n', m' = 0-1 (preferably 0);
j = 0-1(preferably 1);
h, i = 0-1;
p = 1 - number of nucleophilic residues on the drug.
Preferred Components: The **insulin** drug is **insulin** (preferably human **insulin**) and the **oligomer** is covalently coupled to Lys-B29 of the human **insulin** and has formula -C(O)-(CH2)5-(OC2H4)7-OCH3.

The **insulin** drug is covalently coupled to the polyethylene moiety of the **oligomer** by hydrolyzable bond or to the lipophilic moiety.
Preferred Method: The method further involves:
(a) reacting a monodispersed mixture comprising compounds of formula R2(OC2H4)n1-OH (V) with a methanesulfonyl chloride to provide a monodispersed mixture comprising (II);
(b) reacting a monodispersed mixture comprising compounds of formula R2-OMs (VI) with a monodispersed mixture comprising compounds of formula R3(OC2H4)m-O- X+2 (VII) to provide a monodispersed mixture comprising compounds of formula R3(OC2H4)m-OR2 (VIII); and
(c) reacting (VIII) to provide a mixture comprising (V); or reacting a monodispersed mixture comprising a compound of formula R1(OC2H4)n1-OH (IV) to provide a substantially monodispersed mixture comprising (I).
R3 = benzyl, trityl or THP;
X+2 = positive ion.
The activating of the mixture involves reacting (III) with N-hydroxy succinimide to provide an activated polymer capable of reacting with **insulin** drug.
The reaction of monodispersed mixture of activated polymers with a monodispersed mixture of **insulin** involves reacting the monodispersed mixture of activated polymers with Lys-B29 of the human **insulin** to provide monodispersed mixture of monoconjugates each comprising human **insulin** coupled to an **oligomer** containing **polyethylene glycol** with m+n1 subunits.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (b) has at least 2, 3 or 4 (preferably at least 5 or 6, especially at least 7) **polyethylene glycol** subunits.
Preferred **Oligomer**: (a) is covalently coupled to an amine function, which is at Lys-B29 of the **insulin.**
(a) comprises a first **oligomer** covalently coupled at Lys-B29 of the **insulin** and a second **oligomer** covalently coupled at N-terminal A1 or N-terminal B1 of the **insulin.**
The drug in synthesis method is a polypeptide.
(a) further comprises a lipophilic moiety optionally covalently coupled to the **polyethylene glycol** (preferably second **polyethylene glycol**).
The **polyethylene glycol** moiety is covalently coupled to the lipophilic moiety.
The first and the second **oligomers** are the same.
(a) comprises a first **polyethylene glycol** moiety covalently coupled to the **insulin** drug by a non-hydrolyzable bond and a second **polyethylene glycol** covalently coupled to the first **polyethylene glycol** moiety by a hydrolyzable bond.

L10 ANSWER 6 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-167296 [16] WPIDS
DNC C2003-043431
TI Monodispersed mixture of conjugates useful in the treatment of growth hormone deficiency, comprises growth hormone drug coupled to an oligomer containing polyalkylene glycol.
DC A25 A96 B04
IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L; PRICE, C H
PA (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2002098452 A1 20021212 (200316)* EN 73
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ

NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

US 2003027995 A1 20030206 (200318)
EP 1404361 A1 20040407 (200425) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2004004693 A 20040113 (200434)

ADT WO 2002098452 A1 WO 2002-US17504 20020604; US 2003027995 A1 US 2001-873757 20010604; EP 1404361 A1 EP 2002-737344 20020604, WO 2002-US17504 20020604; KR 2004004693 A KR 2003-715911 20031204

FDT EP 1404361 A1 Based on WO 2002098452

PRAI US 2001-873757 20010604

AB WO 200298452 A UPAB: 20030307

NOVELTY - A substantially monodispersed mixture of **conjugates** comprises a growth hormone drug coupled to an **oligomer** containing a polyalkylene glycol moiety.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for synthesizing the substantially monodispersed mixture of **conjugates** involving:

(1) reacting a substantially monodispersed mixture containing compound of formula R1(OC2H4)m-O-X+ (I), with a substantially monodispersed mixture comprising a compound of formula R2(OC2H4)n1-OMs (II) to provide a monodispersed mixture comprising polymers of formula R2(OC2H4)m+n1-OR1 (III);

(2) activating (III) to provide a monodispersed mixture of activated polymers capable of reacting with **insulin** drug; and

(3) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to provide a monodispersed mixture of **conjugates** comprising **insulin** drug coupled to an **oligomer** containing **polyethylene glycol** with m+n1 subunits.

R1, R2 = H or lipophilic moiety;
m, n1 = 1-25;
X+ = positive ion.

ACTIVITY - Osteopathic.

MECHANISM OF ACTION - Growth hormone stimulator.

The activity of growth hormone (GH) GH-002 (test) was evaluated using transcription assay. Stable clones expressing the full-length human growth hormone receptor (GHR) were generated in 293 cells. A transcription assay was performed in 293 GHR cells transiently transfected with a reported construct containing stat5-binding element (LHRE) fused to a minimal TK promoter and luciferase. A beta -galactosidase expression vector was co-transfected as a transfection control and luciferase value corrected for beta -galactosidase activity. Sixteen hours after transfection, cells were transferred into serum free medium and treated with GH or agonist for 6 hours. Luciferase activity was reported as % of maximal activity stimulated by GH. Genotropin was used as the control. The mean fold induction by test was around 225 and for the control was around 25.

USE - The mixture is used in the treatment of growth hormone deficiency in a subject, and for accelerating the growth rate of an animal (claimed). It may also be used in the treatment of osteoporosis and non-healing fractures.

ADVANTAGE - The mixture exhibits greater in vivo activity than the in vivo activity of the polydispersed mixture of **insulin** drug-**oligomer conjugates** having same number of average molecular weight as the mixture. The mixture has increased resistance to

degradation by chymotrypsin, and a lower inter-subject variability.
Dwg.0/30

TECH UPTX: 20030307

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The mixture has molecular weight distribution with a standard deviation of less than 22 (preferably less than 14, especially less than 11) Dalton or dispersity coefficient greater than 10000, especially 500000. In the mixture, the **oligomer** has optionally same number of polyalkylene glycol subunits. When each **conjugate** is the same in the mixture, each **conjugate** has a formula of Growth Hormone Drug-(B'-Lh-Gi-Rm'-G'j-R'n'-Qk-T)p-. The **conjugate** comprises several **oligomers**, which are same. The polyalkylene glycol moiety has at least 2, especially at least 7 polyalkylene glycol subunits. The polyalkylene glycol is uniform polypropylene glycol. The growth hormone drug is human growth hormone. The **oligomer** is covalently coupled to an amine function of the human growth hormone. The drug is covalently coupled to the **oligomer** optionally by a hydrolyzable bond or is coupled to the polyalkylene glycol moiety. The **oligomer** further comprises a lipophilic moiety covalently coupled to the polyalkylene glycol moiety and lipophilic moiety. The lipophilic moiety is covalently coupled to the second polyalkylene glycol moiety. The growth hormone drug is covalently coupled to the lipophilic moiety. The **oligomer** comprises a first polyalkylene glycol moiety covalently coupled to the growth hormone drug by a non-hydrolyzable bond and a second polyalkylene glycol covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond. The **conjugate** is amphiphilically balanced such that the **conjugate** is aqueously soluble and able to penetrate biological membranes. At least 96, 97, 98 or 99% of the **conjugates** in the mixture have the same molecular weight.

B' = bonding moiety;
L = linking moiety;
G, G', Q = spacer moiety;
R = lipophilic moiety or polyalkylene glycol (preferably polyalkylene glycol having at least 7 polypropylene glycol subunits);
R' = lipophilic moiety or polyalkylene glycol;
T = terminating moiety;
h, m' = 0-1;
i, k, n', j = 0-1 (preferably 0);
p = 1 - number of nucleophilic residues on the drug; and
n = number of different molecules in the sample.
Provided that when:
(1) R is polyalkylene glycol, m' is 1; and
(2) R' is polyalkylene glycol moiety, n' is 1.
Preferred Method: The method further involves:
(1) reacting a substantially monodispersed mixture comprising compounds of formula R2(OC2H4)n1-OH (V) with a methanesulfonyl chloride to provide a monodispersed mixture comprising (II);
(2) reacting a monodispersed mixture comprising compounds of formula R2-OMs (VI) with a monodispersed mixture comprising compounds of formula R3(OC2H4)m-O- X+2 (VII) to provide a monodispersed mixture comprising compounds of formula R3(OC2H4)m-OR2 (VIII);
(3) reacting (VIII) to provide a mixture comprising (V); and
(4) reacting a monodispersed mixture comprising a compound of formula R1(OC2H4)n1-OH (IV) to provide (I).
R3 = benzyl, trityl or THP;
X+2 = positive ion.
The activating of the mixture involves reacting the monodispersed mixture of formula (III) with N-hydroxy succinimide to provide an activated polymer capable of reacting with **insulin** drug. The reaction of the monodispersed mixture of activated polymers with a monodispersed

mixture of human growth hormone involves reacting the monodispersed mixture of activated polymers with amino function of amino acid residue of human growth hormone selected from Phe1, Lys38, Lys41, Lys70, Lys115, Lys140, Lys145, Lys158, Lys168 or Lys172 to provide monodispersed mixture of monoconjugates each comprising human **insulin** coupled to an **oligomer** containing **polyethylene glycol** with m+n1 subunits.

L10 ANSWER 7 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-046722 [04] WPIDS
DNC C2003-011825
TI Treatment of diabetes mellitus using an insulin-polypeptide derivative.
DC A96 B04
IN EKWURIBE, N N; FILBEY, J A; PRICE, C H; STILL, J G; ANSARI, A M; ODENBAUGH, A L; RADHAKRISHNAN, B
PA (EKWU-I) EKWURIBE N N; (FILB-I) FILBEY J A; (PRIC-I) PRICE C H; (STIL-I) STILL J G; (NOBE-N) NOBEX CORP
CYC 101
PI WO 2002065985 A2 20020829 (200304)* EN 114
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003050228 A1 20030313 (200321)
AU 2002244020 A1 20020904 (200427)
EP 1409006 A2 20040421 (200427) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002065985 A2 WO 2002-US4440 20020214; US 2003050228 A1 Provisional US 2001-269198P 20010215, US 2002-75097 20020213; AU 2002244020 A1 AU 2002-244020 20020214; EP 1409006 A2 EP 2002-709541 20020214, WO 2002-US4440 20020214
FDT AU 2002244020 A1 Based on WO 2002065985; EP 1409006 A2 Based on WO 2002065985
PRAI US 2002-347713P 20020111; US 2001-269198P 20010215; US 2002-75097 20020213
AB WO 200265985 A UPAB: 20030117
NOVELTY - Treatment of diabetes mellitus comprises orally administering an insulin-polypeptide derivative (I) to a patient within one hour of ingestion of a meal so that it provides an insulin drug concentration in portal vein blood between 10 and 1,000 U/ml within about 60 minutes of administration .

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the use of (I) in the manufacture of an oral medicament for the treatment of diabetes mellitus.

ACTIVITY - Antidiabetic.

Pancreactomized and normal, fasted dogs were orally administered with a polydispersed mixture of insulin polypeptide -NH-C(O)-(CH2)5(OC2H4)7OCH3 (1 mg/kg). At the given dosage of the insulin, all the dogs required glucose rescue, due to marked symptomatic hypoglycemia.

MECHANISM OF ACTION - None given.

USE - In the treatment of diabetes mellitus (claimed).

ADVANTAGE - (I) provides an insulin drug concentration in portal vein blood from about 10 - 1000 U/ml in about 60 (preferably 30) minutes of administration; provides maximum insulin drug concentration in peripheral blood in about 60 minutes; stabilizes peripheral glucose concentration to plus or minus 50% of average peripheral glucose concentration in 30 - 60

minutes; clears the bloodstream of a patient in about 4 hours; and reduces hepatic glucose production in a patient by at least 25% in about 90 minutes. At least 25% of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed in about 120 minutes after injection of the meal (all claimed).
Dwg.1a/20

TECH UPTX: 20030117
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (I) is an **insulin** polypeptide-**oligomer conjugate** (preferably amphiphilically-balanced **insulin** polypeptide-**oligomer conjugate** (II)), an **insulin** analog.
The **oligomer** is coupled to the lysine at the B29 position of the **insulin.** The **insulin** analog is Gly-A21, Gly-A21 Gln-B3, Ala-A21, Ala-A21 Gln-B3, Gln-B3, Gln-B30, Gly-A21 Glu-B30, Gly-A21 Gln-B3 Glu-B30, Gln-B3 Glu-B30, Asp-B28, Lys-B28, Leu-B28, Val-B28, Ala-B28, Asp-B28 Pro-B29, Lys-B28 Pro-B29, Leu-B28 Pro-B29, Val-B28 Pro-B29 or Ala-B28 Pro-B29 human **insulin.**
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (II) is present as a monodispersed mixture in a composition and is of formula **insulin** polypeptide-B'-Lj-Gk-R-G'm-R'-G''n-T (III) (preferably **insulin** polypeptide -NH-C(O)-(CH2)5(OC2H4)7OCH3).
B' = binding group (preferably ester, thio-ester, ether, carbamate, thio-carbamate, carbonate, thio-carbonate, amide or urea group or a covalent bond);
L = linker group (preferably alkyl or fatty acid group);
G, G' and G'' = spacer groups (preferably sugar, cholesterol or glycerine group);
R and R' = lipophilic group (preferably 1-28C (preferably 5-7C or 4-14C) alkyl or fatty acid group) or polyalkylene glycol group (preferably **polyethylene glycol** group containing 1 - 50 (preferably at least 2, especially 4 - 10) polyalkylene glycol subunits);
T = terminating group (preferably alkyl or alkoxy); and
j, k, m and n = 0 or 1.

L10 ANSWER 8 OF 8 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-102601 [11] WPIDS
DNC C2001-029994
TI New drug-**oligomer conjugates** facilitate oral delivery of e.g. **insulin**, and can delay the onset of activity or extend the duration of activity of drug in the bloodstream.
DC A96 B04 C03
IN EKWURIBE, N; RAJAGOPALAN, J; RAMASWAMY, M; EKWURIBE, N N; RAJAGOPALAN, J S
PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP; (NOBE-N) NOBEX INC
CYC 95
PI WO 2000078302 A1 20001228 (200111)* EN 69
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
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NO 2001006143 A 20020218 (200228)
BR 2000011772 A 20020402 (200231)
EP 1196157 A1 20020417 (200233) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2001004597 A3 20020515 (200241)
KR 2002012278 A 20020215 (200257)

CN 1368877 A 20020911 (200282)
JP 2003502364 W 20030121 (200308) 68
HU 2002003745 A1 20030428 (200337)
ZA 2001010099 A 20030528 (200341) 80
MX 2002000054 A1 20030701 (200366)
NZ 516109 A 20040430 (200431)

ADT WO 2000078302 A1 WO 2000-US16879 20000619; AU 2000057500 A AU 2000-57500 20000619; US 6309633 B1 US 1999-336548 19990619; NO 2001006143 A WO 2000-US16879 20000619, NO 2001-6143 20011217; BR 2000011772 A BR 2000-11772 20000619, WO 2000-US16879 20000619; EP 1196157 A1 EP 2000-942956 20000619, WO 2000-US16879 20000619; CZ 2001004597 A3 WO 2000-US16879 20000619, CZ 2001-4597 20000619; KR 2002012278 A KR 2001-716204 20011217; CN 1368877 A CN 2000-811540 20000619; JP 2003502364 W WO 2000-US16879 20000619, JP 2001-504366 20000619; HU 2002003745 A1 WO 2000-US16879 20000619, HU 2002-3745 20000619; ZA 2001010099 A ZA 2001-10099 20011207; MX 2002000054 A1 WO 2000-US16879 20000619, MX 2002-54 20011219; NZ 516109 A NZ 2000-516109 20000619, WO 2000-US16879 20000619

FDT AU 2000057500 A Based on WO 2000078302; BR 2000011772 A Based on WO 2000078302; EP 1196157 A1 Based on WO 2000078302; CZ 2001004597 A3 Based on WO 2000078302; JP 2003502364 W Based on WO 2000078302; HU 2002003745 A1 Based on WO 2000078302; MX 2002000054 A1 Based on WO 2000078302; NZ 516109 A Based on WO 2000078302

PRAI US 1999-336548 19990619

AB WO 200078302 A UPAB: 20010224

NOVELTY - Drug-**oligomer conjugates** (I) which include a hydrophilic component and a lipophilic component liked by a hydrolyzable bond, are new.

DETAILED DESCRIPTION - Drug-**oligomer conjugates** (I), (X), (XI), (XII) and (XIII), which include a hydrophilic component and a lipophilic component liked by a hydrolyzable bond, are new.

D = therapeutic drug moiety;

H, H' = hydrophilic moieties selected from straight or branched **polyethylene glycol** (**PEG**) polymers which have 2-130 ethylene glycol subunits and sugars;

L = lipophilic moiety selected from 2-24C alkyl groups, cholesterol and fatty acids;

m + n + p = at least one, but does not exceed the total number of covalent bonding sites on D for the substituents H', L and H-L;

o (defined in the disclosure) = 1 to the maximum number of covalent binding sites on H; and

L' (defined in the disclosure) = L.

INDEPENDENT CLAIMS are included for:

(1) drug-**oligomer conjugate** of formula (XI), in which the S-L and/or S-H bond is hydrolyzable;

(2) drug-**oligomer conjugates** of formula (XII), in which the S-H and/or S-H' bond is hydrolyzable;

(3) drug-**oligomer conjugates** of formula (XIII), in which the H-H' bond is hydrolyzable;

(4) drug-**oligomer conjugates** of formula (X), in which the H-H' bond is hydrolyzable; and

(5) method of providing to a subject an active drug-**PEG conjugate** of formula (X), in which the H-H' bond is hydrolyzable and the H'L bond is not hydrolyzable, D is **insulin** or a derivative, where (X) has enhanced activity compared to unconjugated **insulin**.

S = spacer group selected from sugars, carbohydrates and glycerol;

n = 1 to the maximum number of covalent binding sites at which S can be attached to H;

o = 1 to the maximum number of covalent binding sites at which L can be attached to S;

p = 1 to the maximum number of covalent binding sites at which ((H-Sn)Lo)p can be attached to D; and

q = 1 to the maximum number of covalent binding sites at which H' can be attached to S.

ACTIVITY - Antidiabetic; virucide; antibacterial.

MECHANISM OF ACTION - None given.

USE - The new **conjugates** can be used in treatment or prevention of any disorders which can be treated by the therapeutic drug D, including bacterial and viral infections. Drug D is preferably **insulin**, useful in treatment of diabetes.

ADVANTAGE - The new **conjugates** contain hydrophilic components, lipophilic components and drug components. These components are variously linked such that, upon hydrolysis of hydrolyzable bonds in the **conjugates**, an active drug-hydrophile **conjugate** remains. The **oligomers** are very suitable for oral delivery, while extending the onset of activity of drug-**oligomer conjugate** in the blood stream. The lipophilic component is preferably selected such that the drug component is inactive until the hydrolyzable bond is hydrolysed. Amphiphilic modification of **insulin** improves its lipophilicity and stabilizes it against enzymatic degradation while improving its membrane permeability.

Dwg.0/3

TECH UPTX: 20010224

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred materials: In (I), the D-H and D-H' bonds, when present are non-hydrolyzable. The D-L' bond, when present, is non-hydrolyzable. The D-H and D-H' bonds are especially carbamate, amide or secondary amine bonds. The H-L bond and D-L' bond are especially ester or carbonate bonds. In all the new **conjugates**, D is especially a biologically active polypeptide (especially **insulin**) or an antigen from an organism associated with a disease state. The **polyethylene glycol** component typically contains 2-7 ethylene glycol units, especially 3 ethylene glycol units.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Hydrolyzable **oligomers** can be synthesized e.g. by coupling fatty acid chlorides with an equivalent of **PEG.** Non-hydrolyzable **oligomers** can be synthesized, e.g., by coupling an alkyl bromide with the monosodium salt of an appropriate **PEG.** The **oligomers** can be activated with N-hydroxysuccinimide and coupled to **insulin** (or some other drug).

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